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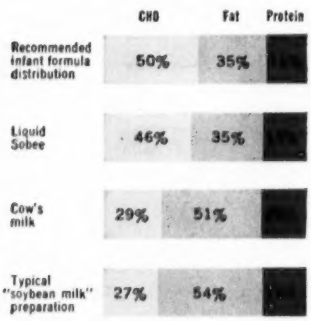

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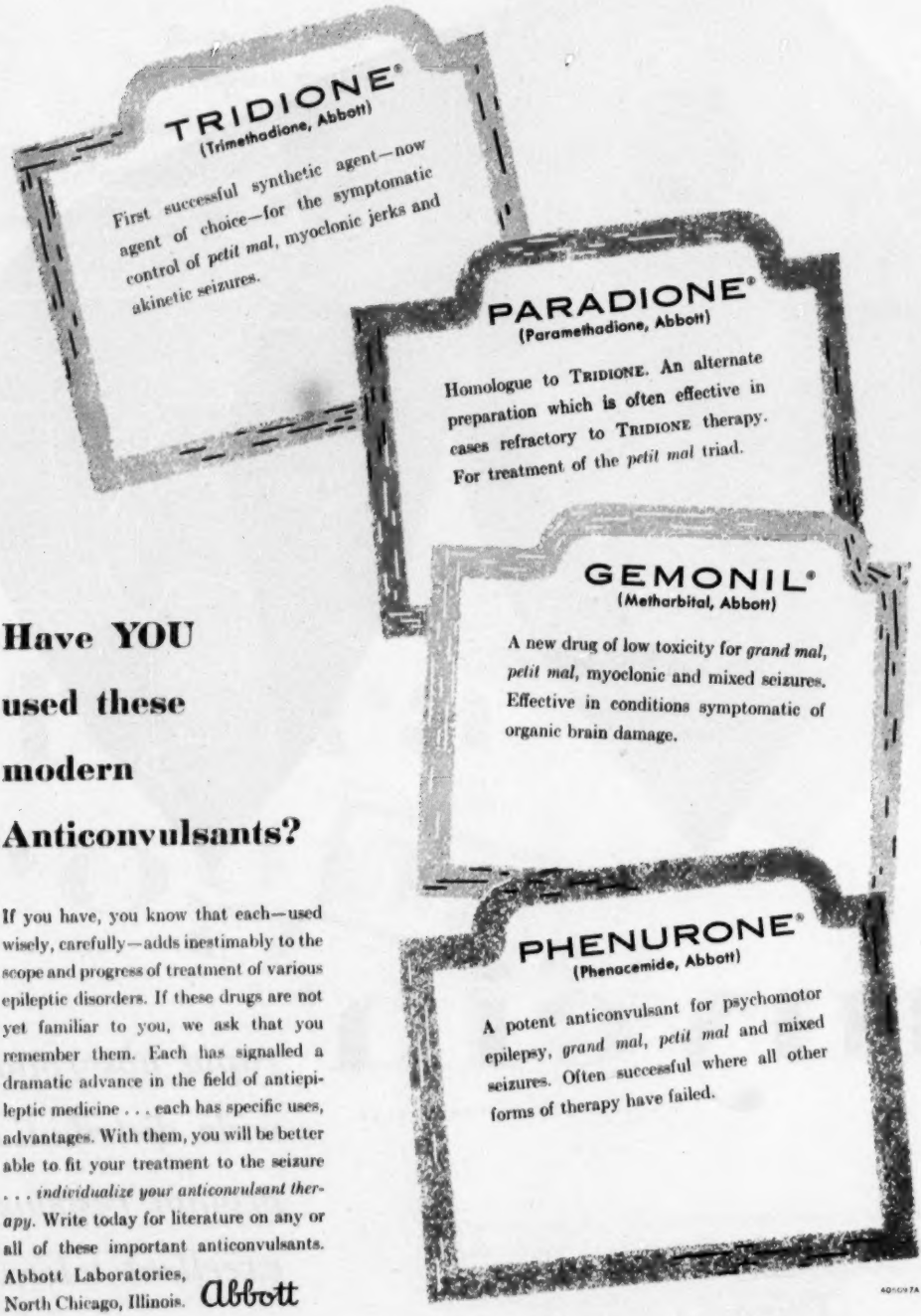
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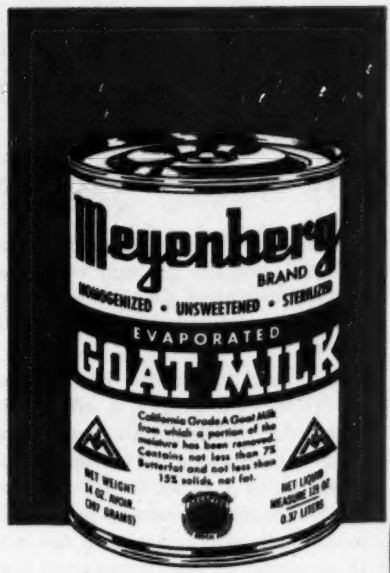
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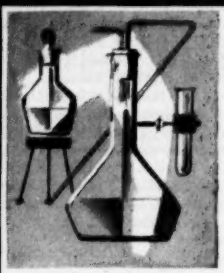

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American Journal of Diseases of Children

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STUDIES ON THE ANEMIA OF PREMATURITY

IRVING SCHULMAN, M.D.
CARL H. SMITH, M.D.
AND
GERTRUDE S. STERN, M.D.
With the Technical Assistance of Eleanor Fort, B.S., Beatrice Bonnem, B.S., and Joyce Prestwidge, B.A.
NEW YORK

ALTHOUGH the anemia of prematurity has long commanded the attention of pediatricians, there still exists a striking lack of agreement concerning most aspects of this syndrome. Many diverse theories relating to the pathogenesis of the anemia of premature infants are still taught, and many diverse modes of prophylaxis and therapy are based upon these theories. Thus the anemia has been variously considered to result from (1) excessive hemolysis,* (2) deficient antenatal stores of hematopoietic factors,[3] (3) bone marrow immaturity,† and (4) rapid growth and hemodilution.[6] The opinions concerning the role of iron in the etiology, prophylaxis, and therapy of the anemia of prematurity are equally variable and range from those which claim no value of iron whatever to those which claim striking benefit.‡ The value of blood transfusion in the management of the anemia of prematurity likewise remains a point of current debate, with widely divergent practices employed in different premature centers.§

A fundamental factor contributing to the lack of agreement has been the dearth of quantitative data relating to blood formation and blood destruction in premature infants. Virtually all studies relating to the anemia of prematurity have depended upon the determination of hemoglobin and red cell concentration, i. e., hemoglobin in grams per 100 ml. of blood and red cell count per cubic millimeter of blood. These values obviously depend not only on the amount of hemoglobin and red cells present in the body at any one time, but also upon the volume in which they are suspended. The latter, in turn, may be dependent upon such variable factors as rate of growth, state of hydration, renal function, presence of illness, and prob-

From Department of Pediatrics of The New York Hospital-Cornell Medical Center.

Presented in part before the Society for Pediatric Research, Atlantic City, N. J., May 4-6, 1953.

This investigation was supported by grants from the National Institute of Arthritis and Metabolic Diseases, United States Public Health Service (RG A-227 [C4]), The Children's Blood Foundation, Inc., and Mead Johnson & Company.

*References 1 and 2.

†References 4 and 5.

‡References 4, 5, 7, and 13.

§References 14 and 15.

ably many others. A quantitative approach to the problem of anemia of prematurity requires, therefore, data concerning total body hemoglobin and total body red cell mass and thus, basically, a knowledge of the blood volume in premature infants. This approach is not at all peculiar to the study of anemia of prematurity, but has, in recent years, assumed increasing importance in the proper quantitative evaluation of all types of anemia in all age groups.‖

The study of the anemia of prematurity, however, does present an additional aspect which requires consideration, namely, the presence in these infants of two distinct types of hemoglobin, fetal and adult. A complete understanding of the anemia of prematurity necessitates, therefore, evaluation of the relationship between these two pigments and their significance in the hematological changes which occur.

It is the purpose of the present investigations to study the quantitative aspects of hemoglobin synthesis and hemoglobin degradation in premature infants, with particular reference to the pathogenesis of the anemia of prematurity. The results will be presented under three headings: (1) fetal and adult hemoglobins in premature infants, (2) blood volume in premature infants, and (3) the mechanism of anemia of prematurity.

I. FETAL AND ADULT HEMOGLOBIN IN PREMATURE INFANTS

IRVING SCHULMAN, M.D.
CARL H. SMITH, M.D.
AND
GERTRUDE S. STERN, M.D.

DIFFERENCES between the hemoglobin of the human fetus and adult have been known since 1866, when Von Korber ¶ demonstrated that fetal hemoglobin was more resistant to denaturation by alkaline solutions than was the adult type. Since then numerous investigations have confirmed the distinction between the two types of pigment and have pointed out physical, chemical, physiological, and immunological characteristics which serve to distinguish one from the other.# Most of the studies have indicated that the differences reside in the globin portion of the molecule, the heme apparently being identical in the two types of hemoglobin.[37]

In recent years Singer, Chernoff, and Singer [38] have modified the method of alkali denaturation so that minute quantities of fetal hemoglobin can be detected with great accuracy. Results obtained in the study of normal infants and children with this more sensitive method have led to revision of previously established concepts. Thus Chernoff and Singer [39] have demonstrated that significant amounts of fetal hemoglobin may persist up to 30 months of age, and in rare persons even up to 4 years. Earlier studies had reported no detectable fetal hemoglobin after 4 to 7 months of age.* Studies of fetal hemoglobin concentrations in premature infants have been very few and have included only a small number of determinations. Jonxis [40] has stated, however, that fetal hemoglobin disappears later in the pre-

‖ References 16-18.

¶ Cited by Bischoff.[19]

References 20-36.

* References 22 and 23.

maturely born infant than in the full-term baby. For this he has given two possible reasons: (1) formation of the fetal hemoglobin postnatally and (2) delay in normal erythrogenesis. Jonxis [41] also believes that the red cells formed after birth in full-term infants normally contain only adult hemoglobin, a fact which has been denied by the previously quoted work of Singer, Chernoff, and Singer.[38] Because of the small number of earlier studies and because of the possibility that the newer method of determination might lead to different results, the investigation of fetal and adult hemoglobin concentrations was undertaken in a large group of premature infants.

MATERIAL AND METHODS

Fetal hemoglobin concentrations were determined exactly as described by Singer and co-workers.[38] In this method an approximate 10% hemoglobin solution is denatured for exactly one minute by N/12 NaOH (pH 12.7), the reaction being halted and the denatured hemoglobin precipitated by addition of a 50% saturated ammonium sulfate reagent. The hemoglobin concentration in the filtrate (undenatured) is determined photoelectrically, and the percentage of undenatured hemoglobin (fetal hemoglobin) is calculated.

As a preliminary part of the investigation, fetal hemoglobin concentrations were determined in the cord blood specimens of 96 normal full-term infants. The blood was taken at time of delivery and was collected in bottles containing dried heparin.

Because of the wide range of fetal hemoglobin concentrations found at birth in full-term babies, it was decided to study premature infants whose birth weight was 2,100 gm. or less. Since the determination of the percentage of fetal hemoglobin is performed on washed erythrocytes, the source of the blood is of no consequence, and samples were taken from vein or heel puncture according to convenience. Samples were taken within the first 24 hours from 36 infants and were repeated at approximately weekly intervals during their stay in the hospital. Following discharge, samples were taken at time of visits to the Premature Clinic at one- to two-month intervals for the remainder of the first year of life. In addition, in order to determine more accurately the disappearance of fetal hemoglobin, random samples were taken in the Premature Clinic on other infants ranging in age from 3 to 12 months. In all, a total of 337 determinations were performed on prematurely born infants during their first year of life. None of the infants upon whom determinations of fetal hemoglobin concentration were performed had received transfusion. Iron was not administered to any of the infants during the first three months of life. Following this point, an oral preparation† of iron was administered to the majority of infants. All infants were fed on a low-fat (Alacta) formula until they had reached a weight of 2,100 gm., at which time evaporated milk formula was substituted. Solid foods were instituted at varying times after the second month of life.

RESULTS

Full-Term Infants.—The distribution of the values for the percentage of fetal hemoglobin at birth in the 96 full-term infants is shown in Figure 1. It may be seen that a wide range of initial fetal hemoglobin concentration was encountered. The values ranged from 44 to 89%; the mean per cent fetal hemoglobin was 71.0, with the S. D. ± 7.7%. No correlation could be determined between the percentage of fetal hemoglobin and the total cord hemoglobin concentration in the full-term infants.

Premature Infants at Birth.—A total of 36 infants were studied in the first 24 hours of life. Of these, 2 were under 1,000 gm.; 14, between 1,000 and 1,499 gm., and 20, between 1,500 and 2,100 gm. at birth. The distribution of the values for the percentage of fetal hemoglobin in the first 24 hours of life is demonstrated in Figure 1. It may be seen that the range of fetal hemoglobin concentration in this

† Fer-in-sol (Mead Johnson & Company).

group is much narrower than that encountered in the full-term infants. The values ranged from 73 to 89%; the mean per cent was 81.1, with the S. D. ± 4.7%. The differences between the premature and full-term infants are statistically significant. Within this group of 36 infants no correlation could be detected between the percentage of fetal hemoglobin present at birth and either the birth weight or the estimated length of gestation.

Disappearance of Fetal Hemoglobin in Premature Infants.—Singer, Chernoff, and Singer [38] have demonstrated that values of fetal hemoglobin in excess of 2% are statistically highly significant in indicating the presence of fetal hemoglobin in normal persons. In studies of normal infants and children, therefore, values below 2% were considered to represent the absence of fetal hemoglobin, while values in excess of 2% indicated persistence of the embryonic pigment.[39] In order to compare disappearance rates in premature and full-term infants in the present

TABLE 1.—*Disappearance of Fetal Hemoglobin in Premature Infants*

Age Period, Mo.	No. Samples Examined	Samples Containing Less than 2% Fetal Hemoglobin	
		No.	% of Total
0-5	279	1	0.035
6-7	31	9	29.0
8-9	12	8	66.6
10-12	14	11	78.6

TABLE 2.—*Comparison of Disappearance of Fetal Hemoglobin in Full-Term and Premature Infants in the Age Period of Seven to Twelve Months*

Group Studied	No. Specimens Examined	Specimens Containing Less than 2% Fetal Hemoglobin		Maximum Value of % Fetal Hemoglobin in Group
		No.	% of Total	
Full-term (Chernoff & Singer [39])	25	6	24.0	27.2
Premature	40	26	64.9	8.3

study, the value of 2% fetal hemoglobin or below was considered to indicate complete disappearance of fetal hemoglobin and complete replacement by adult hemoglobin. The results of 337 determinations in prematurely born infants during the first year of life are shown on a scattergram in Figure 2. It may be seen that up to the age of 6 months only 1 sample out of 279 contained less than 2% fetal hemoglobin. In the subsequent months, however, the proportion of samples containing less than 2% fetal hemoglobin increased progressively. This is shown by the data in Table 1. It may be noted that in the 10- to 12-months age group 78.6% of the determinations revealed absence of significant amounts of fetal hemoglobin. The maximum value for fetal hemoglobin encountered in the latter age period was only 4.5%.

Of great significance is the comparison of the values found in the premature infants with those found by Chernoff and Singer [39] in full-term babies. This is shown in Table 2. It may be seen that in the 7- to 12-months age period fetal hemoglobin concentrations below 2% were found in only 6 of 25 full-term infants examined (24%). In the same age period fetal hemoglobin concentrations below

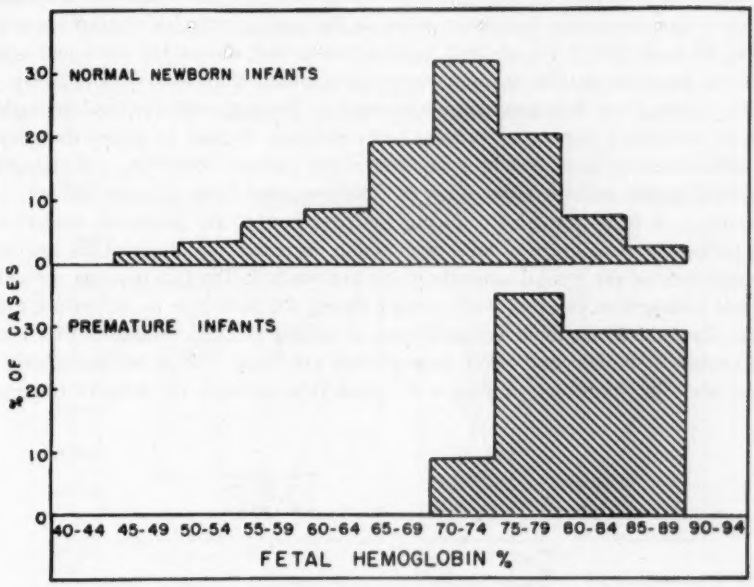

Fig. 1.—The distribution of values for the percentage of fetal hemoglobin present at birth in normal full-term infants and in premature infants.

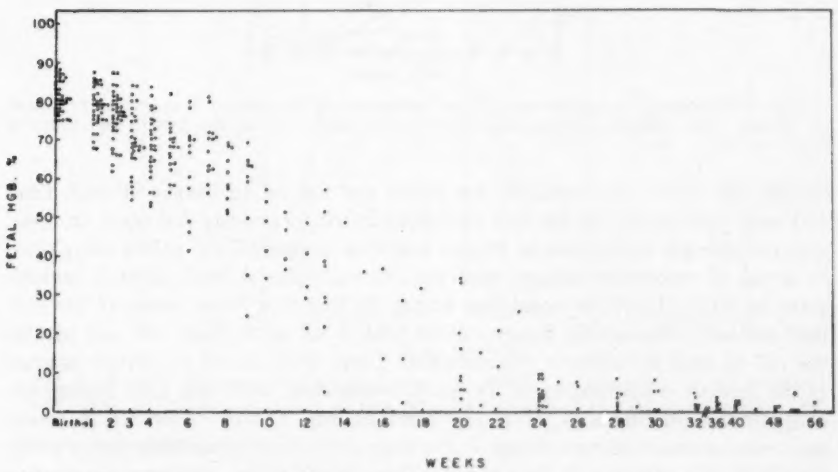

Fig. 2.—Changes in the percentage of fetal hemoglobin in the blood of prematurely born infants during the first year of life.

2% were found in 26 of 40 premature infants examined (64.9%). In the full-term infants values as high as 27.1% fetal hemoglobin were encountered, whereas in the same age period the maximum value in the prematurely born infants was only 8.3%. Thus it would appear that contrary to earlier claims the fetal hemoglobin tends to disappear earlier in prematurely born infants than in full-term babies.

In Figure 3 are demonstrated the changes in the percentage of fetal hemoglobin in four individual infants of varying birth weights. It may be noted that despite the differences in birth weight a fairly uniform pattern describing the changes in fetal hemoglobin concentration emerges. There appears to be minimal change in the percentage of fetal hemoglobin during the first four to six postnatal weeks; after this period the percentage of fetal hemoglobin decreases rapidly until the low levels characteristic of the second semester of life are reached. The fact that the percentage of fetal hemoglobin remains fairly steady during the first four to six weeks, a time when the total hemoglobin concentration is falling steadily, indicates that during this period both fetal and adult hemoglobins are being lost at approximately the same rate. This is shown in Figure 4, which demonstrates the relative changes in

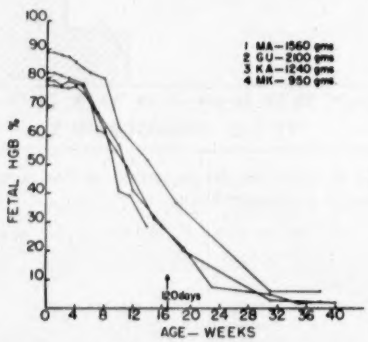

Fig. 3.—Changes in the percentage of fetal hemoglobin in the blood of four premature infants of varying birth weights. Despite the differences in birth weight, the pattern of change is similar in all.

weight and in the concentrations (in grams per 100 ml. of blood) of total, fetal, and adult hemoglobins in the four premature infants previously described. In order that the changes in the several infants might be compared, the values are plotted in terms of percentage change, with the original value at birth of each variable taken as 100%. It will be noted that during the first four to six weeks of life both fetal and adult hemoglobin concentrations tend to fall at the same rate and parallel the fall in total hemoglobin concentration. There then occurs an abrupt increase in the relative concentration of the adult hemoglobin, while the fetal hemoglobin concentration continues to fall at the previous rate. Shortly thereafter, however, there also occurs an abrupt change in the slope of the fetal hemoglobin curve, which then falls at a slower rate than earlier. This change in the relative concentration of fetal hemoglobin at a time when the relative concentration of adult hemoglobin is increasing must mean that the fetal pigment is actually being synthesized at this time. Were it not so, the relative increase in adult hemoglobin concentration would have displaced the fetal hemoglobin curve in exactly the opposite direction. The rate of production of fetal hemoglobin at this point still does not keep pace with

the rate of destruction, since the curve still declines, indicating net loss of the pigment. The changes in relative concentration described above must represent gain in total body hemoglobin, since, as noted in Figure 4, the hemoglobin concentration levels off despite continuing weight gain. Further examination of Figure 4 also demonstrates that the rate of fall of adult and fetal hemoglobin concentrations in the first four to six weeks is more rapid in smaller infants than in larger;

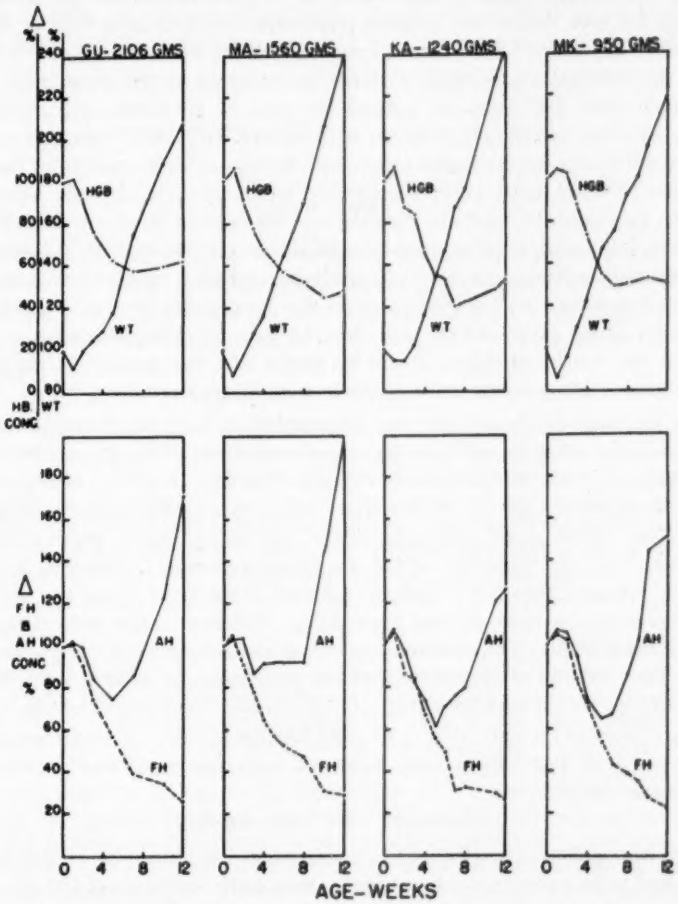

Fig. 4.—Relative changes in weight and in the concentration (in grams per 100 ml. of blood) of total, fetal, and adult hemoglobins in four premature infants of varying birth weights. The value of each variable at birth was taken as 100%, and the subsequent changes were expressed in terms of percentage change.

conversely, the rate of gain of adult hemoglobin concentration during the later weeks is slower in the smaller infants than in the larger. Comparison of rates of weight gain at comparable periods indicates that this, too, is not merely a function of growth and hemodilution. These concepts will be expanded in the succeeding parts of this article.

COMMENT

The present studies indicate several important points relative to the physiology of the fetus and the prematurely born infant. The fact that the full-term infant is born with a greater percentage of adult hemoglobin than the premature is not surprising and indicates that replacement of the embryonic pigment begins in advance of birth. The studies in the prematurely born babies demonstrate, however, that the replacement probably begins early in, or even before, the last trimester of gestation, for even in the very smallest premature infants at least 10% of the adult hemoglobin was found. Still, both premature and full-term infants obviously synthesize the embryonic pigment after birth, as indicated by the persistence of fetal hemoglobin after 120 days, the normal life span of an erythrocyte. Although a striking decrease in the concentration of both fetal and adult hemoglobins occurs during the first four to six weeks (Fig. 4), it is impossible to state from these data the extent to which these changes represent actual loss in total body hemoglobin. It is also impossible to estimate whether any hemoglobin synthesis is taking place at all at this time and, if so, at what rate. However, the fact that the abrupt changes in the relative concentrations of fetal hemoglobin and adult hemoglobin occur during a period of sustained weight gain indicates that hemoglobin synthesis is accelerated at least from this point onward and that net gain of hemoglobin mass is taking place. In the studies to follow it will be shown that the changes in the first six weeks do, indeed, represent marked loss in total hemoglobin mass.[42]

The postnatal production of fetal hemoglobin in both the premature and the full-term infant must be only a temporary phenomenon, since the pigment eventually disappears from the circulation entirely. The fact that fetal hemoglobin disappears at an earlier age in the premature infant than in the full-term baby would seem rather paradoxical, since one might reasonably expect persistence of an embryonic form of metabolism in the immature organism. Chernoff and Singer [39] have demonstrated that half of full-term infants in the 1- to 2-year age period still show significant amounts of fetal hemoglobin. Although comparable studies were not performed in premature infants, the trends demonstrated in the present group suggest that persistence of fetal hemoglobin production for as long a period would be unlikely in the premature infant. If the changes represented by the full-term infant are taken as the normal, it is possible that the inability to synthesize adequate amounts of fetal hemoglobin may represent a specific physiological handicap of the premature infant.[42]

SUMMARY AND CONCLUSIONS

Fetal hemoglobin concentrations were determined at birth in 96 normal full-term infants and in 36 prematurely born infants with birth weights of 2,100 gm. or less. In addition, a total of 337 determinations of fetal hemoglobin concentration were made in premature infants during the first year of postnatal life.

Although prematurely born infants have a higher percentage of fetal hemoglobin at birth, they tend to lose fetal hemoglobin at an earlier age than the full-term babies. Both premature and full-term infants, however, synthesize fetal hemoglobin postnatally.

The concentrations of fetal and adult hemoglobins in the premature infant appear to decrease at the same rate for the first four to six weeks of life. At this point there occurs a sharp increase in the relative concentration of adult hemo-

globin and an abrupt deceleration in the rate of fall of fetal hemoglobin. These phenomena suggest a pronounced increase in hematopoietic activity at this time.

The fall in fetal and adult hemoglobin during the first four to six weeks appears to be more rapid in premature infants of lower birth weight than in larger infants, while the rate of adult hemoglobin increase in the subsequent weeks is slower in the former group than in the latter. These changes appear to be independent of rate of weight gain.

The inability of the premature infant to synthesize fetal hemoglobin in an amount equal to that of the full-term infant may represent a physiological handicap of prematurity.

II. THE BLOOD VOLUME IN PREMATURE INFANTS

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IN PART I of this article it was pointed out that a definitive approach to the problem of the anemia of prematurity requires quantitative data concerning total body hemoglobin and red cell content and that basic to such measurements is knowledge of the blood volume of the premature infant. In the present study this aspect was investigated.

MATERIALS AND METHODS

Blood volume determinations were performed in 38 prematurely born infants ranging in age from 1 to 94 days. The birth weights of these infants ranged from 1,070 to 2,300 gm., and the weights at the time of blood volume estimation, from 1,270 to 3,800 grams. The infants studied had presented an uncomplicated course in the premature nursery and had given no evidence of infection or of disturbance in hydration or nutrition. Transfusions had not been given to any of the infants studied. The determinations were performed three hours after a feeding; all infants were on a low-fat formula (Alacta), and lipemia rarely constituted a problem.

Plasma volumes were determined with Evans Blue dye (T1824) by a modification of the method of Nitshe and Cohen.[43] The dye was made up in sterile ampules in a concentration of 0.1%, and the dose calculated as 0.3 mg. per kilogram of body weight. The estimated amount of dye for a determination was drawn into a syringe, which was then weighed on an analytical balance together with a sterile needle in its case. The weighed needle was inserted into the vein, and about 5.0 ml. of blood was withdrawn without stasis into a dry syringe. With the needle still in place, the dye-containing syringe was substituted and the dye injected without rinsing and with care being taken to prevent backflow of blood into the syringe. The needle was then withdrawn and the blood wiped off the outer surface of it. The syringe, needle, and needle case were again weighed, and the absolute amount of dye injected was calculated by weight. It is believed that the accuracy achieved with this method is far greater than with the use of calibrated syringes. Exactly 10 minutes after injection of the dye, a second sample was withdrawn from a different vein. Predye and postdye injection samples were immediately placed in bottles containing dried oxalate mixtures and the plasmas obtained after centrifugation. An individual dye standard was made for each infant by putting a measured amount of the dye used in the determination into a measured amount of the infant's preinjection plasma (0.2 ml. of a 1:50 solution of dye in saline in 2.0 ml. of plasma). The dye constant was calculated by the formula $K = \frac{D}{C}$, where C equals milligrams of dye per milliliter, and D equals optical density. Plasma volume was calculated from the following formula:

$$PV = \frac{\text{milligrams dye injected} \times K}{D_1}$$

D_1 equals the optical density of the postinjection plasma, using the preinjection plasma as a blank. All readings were made in a Coleman Junior Spectrophotometer, using 10 mm. × 75 mm.

cuvettes. The second sample was drawn at 10 minutes, in accordance with the findings that in both adults and in newborn infants complete mixing and minimal loss of dye occurs in this period.‡ The blood volume was calculated from the plasma volume and the venous hematocrit, using the factors stressed by Mollison and co-workers [47] in their studies of blood volume in newborn infants. Thus the hematocrit was first multiplied by 0.95 to correct for trapped plasma. The result was further multiplied by 0.87, the factor expressing the relationship of whole body

TABLE 1.—*The Blood Volume in Premature Infants*

Case No.	Age, Days	Wt., Gm.	Hemoglobin, Gm./100 Ml. Blood	Hematocrit, %	Plasma Volume		Red Cell Volume		Total Blood Volume	
					Ml.	Ml./Kg.	Ml.	Ml./Kg.	Ml.	Ml./Kg.
1	1	1,600	20.6	55.6	91.0	56.8	56.5	35.4	168.0	105.0
2	2	2,064	16.2	48.9	125.9	61.1	86.0	41.7	211.9	102.9
3	3	1,900	16.9	48.7	100.5	52.9	68.1	35.8	168.6	88.7
4	5	2,282	14.1	42.4	168.5	74.5	91.5	40.4	260.0	114.9
5	5	2,180	15.2	47.1	135.0	62.0	108.5	49.7	222.0	101.7
6	6	1,640	21.4	66.7	73.8	45.0	91.7	55.9	165.5	100.9
7	9	1,540	16.7	51.5	111.5	72.4	83.0	53.8	194.5	126.2
8	11	1,600	19.8	55.5	93.9	58.7	81.0	50.6	174.9	109.3
9	12	1,260	16.6	50.0	71.3	56.6	49.7	39.8	121.0	96.5
10	12	1,700	17.1	46.5	81.9	48.2	51.5	30.3	133.4	78.5
11	13	1,762	10.8	31.3	107.7	61.2	37.8	21.5	145.5	82.7
12	14	1,620	17.6	52.3	97.0	59.8	72.5	44.7	171.5	105.8
13	16	1,640	16.6	49.4	93.9	57.2	68.9	41.4	161.8	98.6
14	16	1,850	15.6	42.0	120.6	65.2	64.3	34.8	184.9	99.6
15	17	2,296	15.1	47.2	134.5	58.5	86.5	37.6	221.0	96.2
16	20	2,300	16.3	47.5	131.6	57.2	103.0	44.8	234.6	102.0
17	21	1,600	14.3	38.9	106.1	66.3	60.6	38.8	166.7	104.2
18	22	2,382	14.2	38.2	106.3	44.9	52.4	22.0	159.3	66.9
19	22	1,520	13.3	37.5	85.8	56.4	38.7	25.5	124.5	81.9
20	22	1,600	15.9	47.2	66.2	41.4	42.7	26.1	108.9	68.0
21	24	1,620	12.6	40.3	108.4	63.8	51.8	31.9	155.2	95.8
22	26	1,980	12.5	37.4	87.6	46.1	39.4	20.8	127.0	66.8
23	26	2,380	11.7	35.4	127.8	53.7	53.2	22.4	181.0	76.1
24	28	2,300	9.8	27.3	139.3	60.6	40.9	17.8	180.2	78.3
25	30	1,540	11.4	34.8	91.0	60.5	36.5	24.5	127.5	85.0
26	30	1,850	13.8	41.8	107.2	57.9	56.9	30.8	164.1	88.7
27	32	2,160	10.1	28.2	146.7	67.9	44.5	20.7	191.5	88.7
28	36	2,200	9.0	29.4	140.7	63.9	45.1	20.6	186.1	84.6
29	36	2,150	10.9	33.4	122.7	57.5	47.1	22.0	171.1	79.6
30	41	1,530	9.8	26.4	95.7	62.1	26.8	17.5	122.5	80.0
31	41	3,100	10.1	28.9	166.7	53.8	52.4	16.9	219.1	70.7
32	44	2,120	10.8	25.0	119.7	56.6	31.4	14.8	151.1	71.3
33	44	2,240	12.7	24.9	115.7	51.6	30.2	14.5	145.7	65.1
34	46	1,996	9.0	22.2	138.2	69.2	32.6	16.3	170.8	85.6
35	52	2,300	8.8	27.1	123.3	53.6	28.0	12.2	151.3	65.8
36	60	2,220	9.0	23.7	115.0	52.3	28.2	12.8	143.2	65.1
37	77	3,200	10.1	29.5	192.1	60.0	62.3	19.5	254.4	79.5
38	94	3,800	10.4	30.5	212.3	55.0	71.9	18.9	284.2	74.9

hematocrit to venous hematocrit. It is of great interest that this latter constant, determined in newborn infants with hematocrits ranging from 17.9 to 66.2%, differs very slightly from that found by Gibson and co-workers [48] in human adults and in dogs (0.91). The final formula for total blood volume is, therefore, as follows:

$$\text{Blood volume} = \frac{\text{plasma volume}}{100 - 0.87\ (\text{packed cell vol.} \times 0.95)} \times 100$$

Using the above factors, the values determined by the dye-hematocrit method have been found to agree closely with those obtained using isotope-tagged red cell methods.[47]

‡ References 45-47.

RESULTS

The complete results of the 38 determinations are presented in Table 1, with the cases listed in order of age at the time of the determination. Since the estimations were made in infants of varying weights, the data for blood volume, plasma volume, and red cell volume are expressed in terms of milliliters per kilogram in the analyses discussed below.

A. *Blood Volume.*—Figure 1 demonstrates the relationship between the age of the infant and the blood volume in milliliters per kilogram. In order to describe

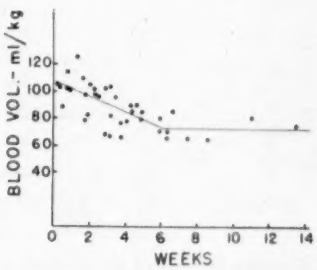

Fig. 1.—Changes in blood volume (milliliters per kilogram of body weight) with age. The regression line describing the changes in the first six weeks is based on the equation of $Y = 94 + [-0.83\ (x - 16.8)]$. The slope of this regression line is statistically significant; $r = -0.605$; $P < 0.01$.

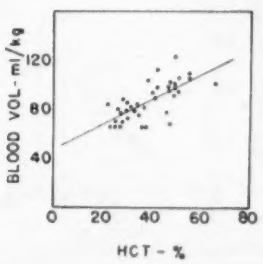

Fig. 2.—The relationship between venous hematocrit and blood volume (milliliters per kilogram of body weight). The solid line is a calculated regression line, the equation of which is $Y = 88.3 + 0.99\ (x - 38.8)$. The slope of the line is statistically significant; $r = 0.67$; $P < 0.01$.

the data, sectional regression equations were calculated. These regression lines thus determined are shown in Figure 1. The slope seen to occur during the first six weeks of life was found to be statistically highly significant (corr. coeff.: $r = -0.605$; $P < 0.01$). From the 7th to the 14th weeks, however, no significant slope could be detected. Thus the premature infant seems to begin life with a blood volume of about 108 ml. per kilogram. This falls steadily during the first six postnatal weeks and then levels off at about 73 ml. per kilogram.

Figure 2 demonstrates the relationship between venous hematocrit and the blood volume in milliliters per kilogram. The individual determinations are repre-

sented by dots and the calculated regression line by the solid line. The slope of the latter line was found to be highly significant ($r = 0.670$; $P < 0.01$). Thus within the limits of hematocrit encountered in this group (22.2-66.7%) there is a definite tendency for the blood volume to vary with the venous hematocrit.

B. *Red Cell Volume.*—In Figure 3 the values for red cell volume in milliliters per kilogram are plotted against the age of the infant. As above, sectional regression equations were calculated, and the regression lines describing the data are shown. As with the blood volume, a significant slope is seen during the first six weeks of postnatal life ($r = -0.753$; $P < 0.01$). From the 7th to the 14th week no significant slope could be detected. Thus the red cell volume at birth appears to be about 46 ml. per kilogram; it then falls steadily during the first five to six weeks to about 16 ml. per kilogram, at which point it tends to level off.

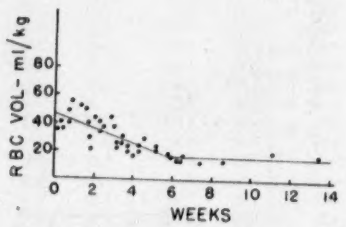

Fig. 3.—Changes in red cell volume (milliliters per kilogram of body weight) with age. The regression line describing the changes in the first six weeks is based on the equation $Y = 32.7 + [-0.76\ (x - 19.3)]$. The slope of the line is significant; $r = -0.753$; $P < 0.01$.

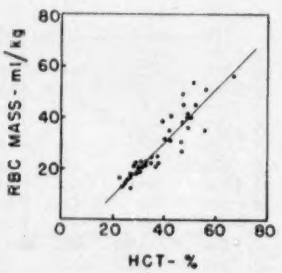

Fig. 4.—The relationship between venous hematocrit and red cell volume (milliliters per kilogram of body weight). The solid line is derived from the regression equation $Y = 29.2 + 1.04\ (x - 38.8)$. The slope of the line is statistically significant; $r = 0.91$; $P < 0.01$.

Figure 4 demonstrates the relationship between venous hematocrit and red cell volume. It will be noted that within the range of hematocrit studied the relationship is linear ($r = 0.91$; $P < 0.01$). Thus the red cell volume varies directly with the venous hematocrit. However, since only one value for venous hematocrit over 60% was encountered, the changes in the latter range cannot be properly evaluated.

Plasma Volume.—Figures 5 and 6 demonstrate the relationship of the plasma volume to the age of the infant and to the venous hematocrit, respectively. Con-

trary to the findings with total blood volume and with red cell volume, the plasma volume seemed to be independent of the two variables, and no definite trends could be determined. During the first six weeks of life, values for plasma volume ranging from 45 to 74.5 ml. per kilogram were encountered. In the subsequent weeks rather large variations in plasma volume were likewise found. However, if the values along the regression line for red cell mass are subtracted from those for blood volume, the results indicate that the plasma volume averages about 62 ml. per kilogram at birth and falls to a level of about 55 ml. per kilogram during the second month of life. These changes are not statistically significant.

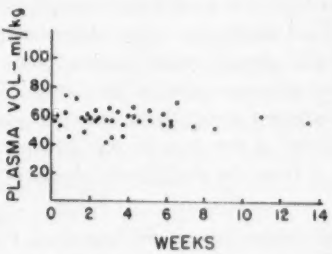

Fig. 5.—The relationship of age to plasma volume (milliliters per kilogram of body weight). No significant relationship could be demonstrated.

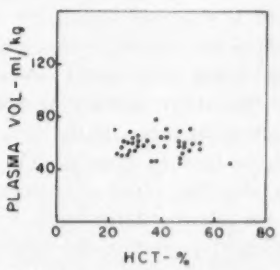

Fig. 6.—The relationship of venous hematocrit to plasma volume (milliliters per kilogram of body weight). No significant relationship could be demonstrated.

COMMENT

The estimation of blood volume by the dye-hematocrit method presents possible sources of error which should be stressed. The basic determination is that of the plasma volume, which depends upon calculation of the dilution of a specific amount of injected dye which is assumed to be uniformly distributed in the plasma. In the present study the sample of blood upon which dye dilution was determined was taken 10 minutes after injection of the dye. The use of a single 10-minute specimen has been in common use since the work of Noble and Gregersen,[45] which demonstrated that in the normal adult complete mixing and minimal loss of dye occurs in that time interval. Mollison and co-workers [47] also employed the 10-minute sample and found satisfactory agreement between values for red cell volume obtained by the dye-hematocrit method and those obtained with the use of radiophosphorous-

tagged red cells. These prior studies, however, do not guarantee that a similar situation exists in the premature infant. If dye is lost more rapidly from the circulation, the values for plasma volume, red cell volume, and total blood volume would be falsely high. If, on the other hand, the mixing time is slower in the premature infant, the opposite effect, namely, falsely low values, would result. Since it was not feasible to make direct determinations of mixing and disappearance times of the dye in the premature infants studied, these factors must, at present, be considered possible sources of error in the measurements presented.

It is apparent that the data presented in this study can do no more than indicate suggestive trends. The determinations were performed on prematurely born infants whose birth weights varied widely, as did their weights and ages, at the time the estimations were made. It is likely that serial determinations of blood volume in individual cases would have given a more precise picture of the changes taking place than do the grouped data presented in this study. However, repeated determinations in a premature infant would have induced anemia and so negated the entire investigation. Analysis of the data in the present study revealed trends of statistical validity, and it is from the statistically significant results that conclusions are drawn.

While wide ranges of values have been found in study of blood volume in normal persons of all ages, it is to be expected that the widest variations would occur in the newborn infant and even more so in the prematurely born infant. Probably the greatest single factor in the newborn, as indicated by the work of De Marsh, Windle, and Alt,[49] is the amount of blood transferred from the placenta to the infant before the cord is clamped. Haselhorst and Allmeling [50] found that the average amount of blood in the placental vessels was 105 cc., with a range of 50 to 200 cc. It was further found that infants received varying amounts of this blood, depending upon the time after delivery at which the cord was clamped. Thus 51% of the blood reached the infant in the first minute after delivery, 79% in 5 minutes, and 91% in the first 10 minutes. The studies by De Marsh and co-workers [49] demonstrated also that rapid adjustments of plasma volume could take place, as indicated by the fact that three hours after birth the plasma volume of infants who had been allowed to receive the placental blood was no different from those who had been deprived of it by early clamping of the cord. It is apparent, therefore, that variations in the amount of placental blood, time of tying of the cord, capacity for adjustment, and the time after birth that the estimations are performed can combine to yield striking variations in the values for blood volume in the newborn infant. Thus, Mollison and co-workers,[47] in a recent carefully performed series of blood volume estimations in newborn infants, found values for total blood volume ranging from 68.0 to 100.3 ml. per kilogram (mean = 84.7 ml. per kilogram).

In the premature infant, still additional factors are involved. Numerous changes normally take place during the third trimester of gestation which may bear important relationships to the blood volume of the prematurely born infants. First, as indicated by studies on human fetuses, the hemoglobin and red cell concentrations, as well as the hematocrit, increase steadily during this period.[51] Second, as demonstrated by Barcroft and Kennedy [52] in studies of sheep fetuses, the ratio of blood volume to body weight declines progressively with gestation, although the absolute

amount of blood increases. Third, the relative amounts of blood in the placenta and in the fetus change with progress of gestation. In regard to the latter, Barcroft and Kennedy [52] found in sheep that while the amount of blood in the placenta remains fairly constant during the third trimester, that in the body increases steadily. Further, the blood is equally divided between placenta and fetus at the beginning of the last trimester of gestation, while at term only about one-fourth of the total blood is in the placenta. These facts, if applicable to the human, would have profound influence on the blood volume of the infant born prematurely. Differences between the premature and full-term infant would be anticipated, as would differences between prematures of varying lengths of gestation. If the blood volumes soon after birth were the same as those in utero, one would expect, as indicated above, that the prematurely born infant would have a greater blood volume per unit of weight than the full-term infant. In addition, the effect of transfer of blood from the placenta to the infant in the minutes after birth would have a far greater relative effect in the prematurely born infant than in the full-term baby. Since the amount of blood in the placenta remains nearly constant during the third trimester of gestation, the prematurely born infant could, theoretically, receive the same amount of blood, through delayed tying of the cord, as the full-term infant. The effect of this transfusion on the blood volume would depend, to a large degree, on the size of the recipient.

The studies here reported indicate that the prematurely born infant begins life with a larger blood volume per unit weight than does the full-term infant. Interestingly enough, however, the red cell mass of about 46 ml. per kilogram does not differ significantly from the average of 43.4 ml. found by Mollison and co-workers [47] in the full-term newborn infant. Thus, in the premature baby, the increased blood volume appears to be related to relative excess of plasma volume.

Despite variations found in the neonatal period, the evidence indicates that the full-term and premature infants soon adjust the blood volume to a range which, under normal circumstances, is maintained for the remainder of life. In a group of 24 infants ranging in age from 1 to 23 months, McIntosh,[53] using the carbon monoxide method, found an average blood volume of 77 ml. per kilogram. Russell,[54] in 10 infants from 3 to 11 months of age, found an average blood volume of 78.7 ml. per kilogram. In the studies of Brines, Gibson, and Kunkel,[55] the seven infants ranging in age from 19 days to 1 year gave an average blood volume of 73.6 ml. per kilogram. In adults, Reeve and Veall [56] found average blood volumes of 76.6 ml. per kilogram, while Gibson and Evans [44] found 77.5 ml. per kilogram. In the group of premature infants studied here, the blood volume appears to have leveled off at about 73 ml. per kilogram after the second month of life.

The relationship shown here between venous hematocrit and both red cell and total blood volumes in milliliters per kilogram are similar to the findings of Mollison and co-workers [47] in full-term infants. The latter authors, however, found an inverse relationship between venous hematocrit and plasma volume, which was not demonstrated in the present studies. Whether this represents a defect in the capacity for plasma volume adjustment on the part of the premature infant cannot be stated with certainty.

SUMMARY AND CONCLUSIONS

Blood volume estimations were made on 38 prematurely born infants ranging in age from 1 to 94 days.

The results indicated that the premature infant begins life with a relatively high blood volume (108 ml. per kilogram), which falls steadily to about 73 ml. per kilogram by the seventh week of postnatal life.

The red cell volume at birth was estimated to be 46 ml. per kilogram at birth. This fell steadily and reached the level of 16 ml. per kilogram by the seventh week.

Both red cell volume and total blood volume tended to vary directly with the venous hematocrit. No such relationship could be demonstrated between the plasma volume and the venous hematocrit.

The reasons for variations in blood volume and for differences between premature and full-term infants are discussed.

III. THE MECHANISM OF THE ANEMIA

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AND
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AS MENTIONED in the introduction, the purpose of these investigations has been to obtain quantitative data concerning hemoglobin synthesis and hemoglobin loss in premature infants and to evaluate the significance of these factors in the pathogenesis of the anemia of prematurity. Necessary prerequisites for this study were the estimations of the total blood volume and of the proportions of fetal and adult hemoglobins in premature infants. These were reported in the first two parts of this article. With the data now at hand it becomes possible to evaluate the changes in total body hemoglobin and in its component parts without implicating the many variables influencing the hemoglobin concentration in grams per 100 ml. of blood.

METHOD OF APPROACH

The infants studied consisted of 32 prematurely born infants whose birth weights were 2,100 gm. or less. On each infant, samples of blood were taken by heel puncture in the first 24 hours of life and at weekly intervals during its stay in the hospital. Following discharge, samples were taken in the Premature Clinic at one- to two-month intervals during the first year of life. Determinations performed on these blood specimens consisted of hemoglobin concentration (photoelectric), red cell count, reticulocyte count, and estimation of the percentage of fetal hemoglobin according to the method previously described.[38] The weights of the infants were recorded at the time of each sampling. Since repeated blood volume determinations would have induced anemia, the blood volume estimations (T1824) were made on 38 different premature infants, ranging in age from 1 to 94 days, as described in Part II. In the present study, the values for blood volume were taken from the calculated regression lines representing the changes in blood volume in milliliters per kilogram as a function of age. At each age that a blood sample was taken, the value for blood volume in milliliters per kilogram was derived from the regression line. This value, when multiplied by the infant's weight, yielded the value for total blood volume; multiplication of the total blood volume by the hemoglobin concentration (in grams per 100 ml. blood) yielded the total hemoglobin mass; multiplication of the total hemoglobin mass by the percentage of fetal hemoglobin allowed calculation of the component parts of fetal and adult hemoglobins. With the values for red cell count and blood volume, it was also possible to make estimations of total body red cell content at various periods. Study of body erythrocyte content was not stressed in these investigations, due to the large errors known to be inherent in red cell counting.

It is realized that estimation of blood volume from the regression line immediately presents a possible source of error in drawing conclusions from the data. However, as indicated before, it is impossible with the methods available to perform repeated blood volume determinations on premature infants over a period of months without inducing anemia. The data from which the regression lines were derived were obtained on a group of premature infants comparable to those in the present study, and the regression lines themselves were found to be statistically significant. In addition, it was felt that the studies were carried out at sufficiently frequent intervals and over a sufficiently long period to cancel out minor deviations in individual cases and to indicate definite trends. Finally, as will be shown below, the results obtained in this study logically explain many of the phenomena in the anemia of prematurity and are supported by the results

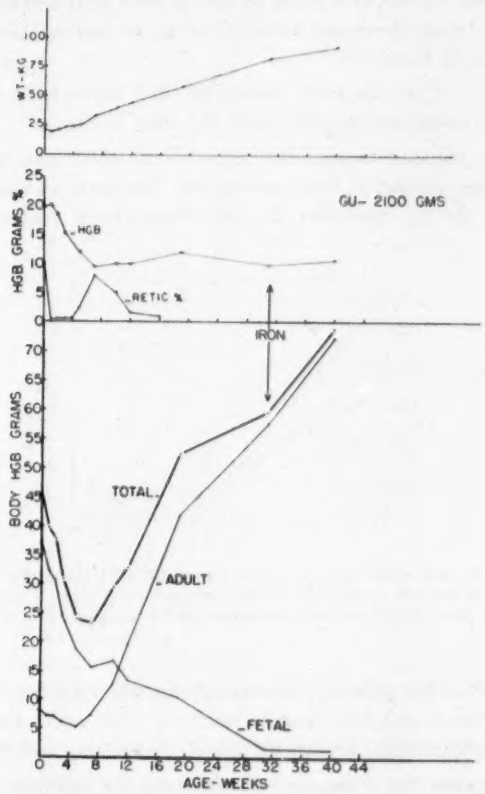

Fig. 1.—Changes with age in weight, hemoglobin concentration, reticulocyte count, and body hemoglobin content (total, fetal, and adult) in a premature infant whose birth weight was 2,100 gm.

of several other independent investigations. The striking uniformity of the indicated trends in the 32 cases studied has led us to believe, with a fair degree of assurance, that the interpretations are valid.

RESULTS

Because of the number of factors indicated in these studies, it was believed that the greatest clarity of presentation could be achieved by demonstrating the complete courses of representative cases. For this purpose the changes in four infants of varying birth weights (2,100, 1,240, 950, and 1,560 gm.) will be shown. As will

be noted, the sequence of events is fairly uniform despite the differences in birth weight. The pattern which emerges was quite constant in the group of 32 infants of which the four shown are typical.

Infant Gu (Birth Weight 2,100 Gm. [Fig. 1]).—In Figure 1 are shown the changes with time in hemoglobin concentration, reticulocyte count, body hemoglobin content (fetal, adult, and total), and weight. The following points may be noted:

(*a*) During the first five weeks of postnatal life there occurred a steady decrease in body hemoglobin content as a result of loss of both fetal and adult hemoglobins. During this same period there was a steady fall in the hemoglobin concentration in grams per 100 ml. of blood.

(*b*) At 5 weeks of age the body content of adult hemoglobin began to increase sharply, this gain continuing steadily until the 18th week.

(*c*) Soon after the adult hemoglobin began to rise, there also occurred a definite increase in the body content of fetal hemoglobin. The latter increase, however, was unsustained, and shortly thereafter the fetal hemoglobin content again declined steadily.

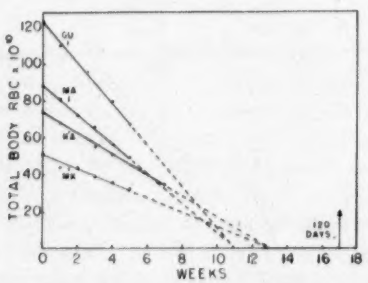

Fig. 2.—Changes in total body red cell content during the first six weeks of life, as calculated from blood volume and red cell count. The fall in body red cell content is linear in each instance. Extrapolation of the lines of fall permits estimation of the survival time of the initial red cell population.

(*d*) As a result of the gain in adult hemoglobin, the total body hemoglobin content began to increase and rose steadily until the 18th week. During this period the hemoglobin concentration leveled off despite continuing weight gain.

(*e*) It may be seen that it required 16 weeks for the infant to regain the hemoglobin mass with which he began life. Since iron derived from the destruction of hemoglobin is not excreted from the body,[57] these 16 weeks were characterized by the presence of more iron in the body than was utilized for hemoglobin synthesis. Shortly afterward (at 18 weeks), however, the rate of gain of total body hemoglobin decellerated markedly, an event which was accompanied by a fall in hemoglobin concentration in the blood. With the administration of medicinal iron § the rate of gain of body hemoglobin accelerated, and the hemoglobin concentration again rose.

(*f*) On the first day of life a reticulocytosis of 10% was evident. The reticulocyte count fell sharply to less than 1% at the end of the first week and remained

§ Fer-in-sol (Mead Johnson & Company).

at very low levels during the next four weeks. Coincident with the beginning of gain of adult hemoglobin, a second reticulocyte peak occurred.

(*g*) During the first six weeks of life the fall in total body hemoglobin was linear. In this period it may be calculated that hemoglobin was being lost at the rate of 1.43% per day, as compared with the normal rate of 0.83% per day. The total body red cell count also decreased linearly during this time (Fig. 2), and it may be calculated that the red cells were being lost at the rate of 1.3% per day (normal, 0.83% per day). Extrapolation of this rate of erythrocyte fall as shown on Figure 2 indicates a decreased survival time of the initial red cell population

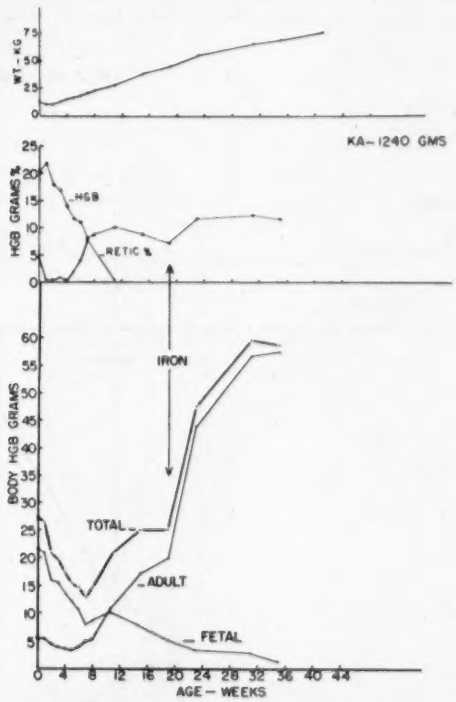

Fig. 3.—Quantitative changes in a premature infant with birth weight of 1,240 gm.

(survival time = 77 days; normal = 100 to 120 days). Thus it would appear that an element of increased rate of hemolysis does, indeed, exist in the premature infant. The reason for the greater rate of fall in hemoglobin than in red cell content will be discussed later.

Infant K. A. (1,240 Gm. [Fig. 3]).—Here, as in the above case, the same sequence of events may be noted. Total body hemoglobin fell steadily during the first seven weeks as a result of loss of both fetal and adult hemoglobins and was represented in the peripheral blood by a fall in hemoglobin concentration. At about 6 weeks of age, gain in adult hemoglobin began and was followed shortly by the sharp but unsustained gain in fetal hemoglobin. Steady increase in total body hemoglobin continued for 16 weeks and then stopped abruptly. The latter event

was manifested by a fall in hemoglobin concentration in the peripheral blood. Administration of iron at the 19th week was followed by striking resumption of hemoglobin gain and by a rapid rise in hemoglobin concentration. A marked reticulocytosis was seen at 7 weeks of age and coincided with the initial onset of

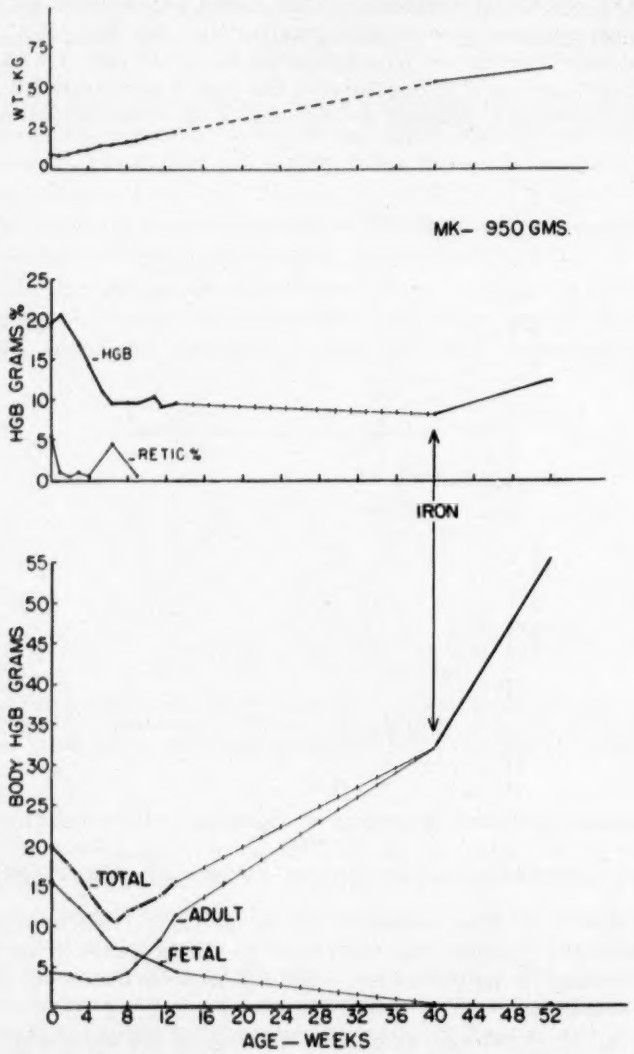

Fig. 4.—Quantitative changes in a premature infant with birth weight of 950 gm.

gain in adult hemoglobin. During the first five weeks of life, total body hemoglobin was lost, in this infant, at a rate of 1.3% per day; total body red cell content decreased at a rate of 1.1% per day, which corresponds to a red cell survival time of 91 days.

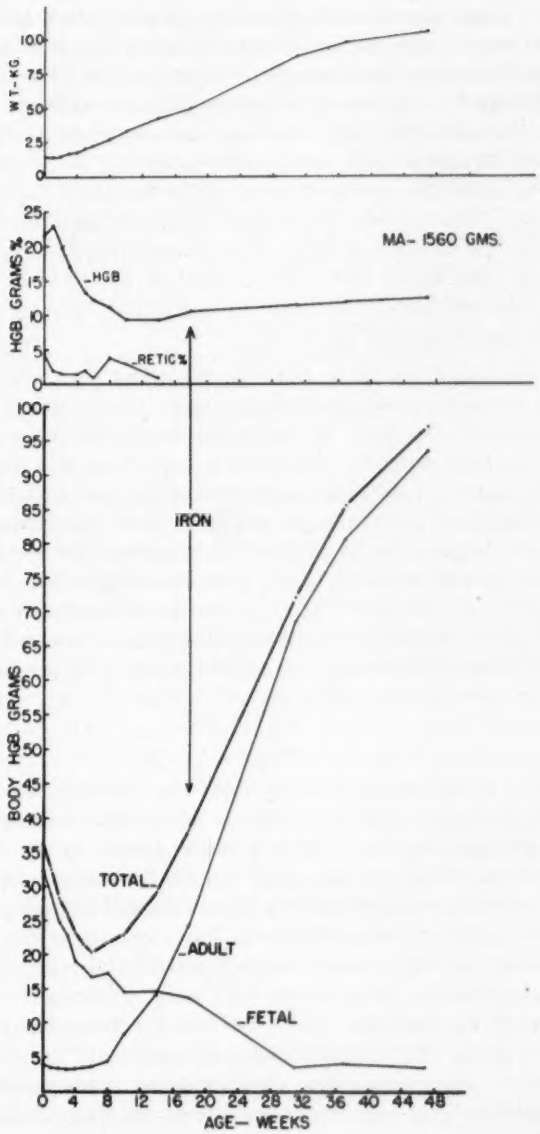

Fig. 5.—Quantitative changes in a premature infant with birth weight of 1,560 gm.

Infant M. K. (950 Gm. [Fig. 4]).—Even in this very small infant the sequence of events during the first three months was almost identical with that shown in the foregoing cases. The fall in hemoglobin content during the first six weeks was followed by a spontaneous onset of hemoglobin gain, which continued steadily during the next seven weeks and which was manifested by a levelling off of hemoglobin concentration despite continuing gain in weight. At 13 weeks of age, this infant was discharged to the care of a private physician and was given no iron and very little iron-containing foods. She was next seen at 40 weeks of age, when she was referred because of pallor and a hemoglobin level of 7.5 gm. per 100 ml. blood. It will be noted that in this 40-week period the infant had gained only 11 gm. of body hemoglobin over the 20 gm. with which she began life, an increase of only 55%. With the administration of iron, prompt recovery occurred. In this baby, hemoglobin loss during the first five weeks of life occurred at the rate of 1.2% per day; red cell content decreased at a rate of 1.1% per day, corresponding to a red cell survival time of 91 days.

Infant M. A. (1,560 Gm. [Fig. 5]).—In this infant the changes in the early months of life were essentially the same as those shown earlier. Here, too, it required 16 weeks for the infant to regain the hemoglobin mass with which he began life. In this baby, however, oral iron was begun at exactly 16 weeks of age. In this case, as contrasted with the others, hemoglobin gain continued unchecked, and the hemoglobin concentration in the peripheral blood continued to rise steadily. At 40 weeks of age this infant's total body hemoglobin had increased by 186% over the amount present at birth. In the three preceding infants the gain at the same time was only 67, 108, and 55%, respectively. During the first five weeks of postnatal life, loss of total body hemoglobin occurred at a rate of 1.43% per day; red cell content in the same period decreased at a rate of 1.3% per day, corresponding to a red cell survival time of 77 days.

COMMENT

As mentioned earlier, the conclusions which may be drawn from the data presented must be tempered by the realization of the possible sources of error. The reliance upon averaged data in order to evaluate changes in one child is always subject to criticism. In the present study the blood volume values used in the calculation of total body hemoglobin were estimated from regression lines obtained in the study of a different group of infants. The necessity for this approach was based upon the fact that with present methods, serial blood volume determinations in an individual premature infant would have induced anemia. In an attempt to overcome some of the objections, the actual blood volume determinations were performed on a group of premature infants comparable to those in the present study. In addition, the grouped data were subjected to statistical analysis, and statistically significant regression lines were determined. The values for total body erythrocyte content, in particular, must be accepted with caution, since these depend not only upon estimation of blood volume but upon determination of the red cell count, a technique with a large inherent error. The estimations of the life span of the erythrocyte in premature infants must, therefore, be considered tentative at best.

Despite the above reservations, however, the derived data, in conjunction with study of hemoglobin concentration, reticulocyte counts, fetal and adult hemoglobin relationships, and response to iron, indicate certain definite trends and patterns of theoretical and practical interest.

As a result of these studies, it appears that the major physiological alteration underlying the developments of anemia of prematurity is a striking depression of hematopoietic activity soon after birth. This is strongly indicated by the fact that the reticulocyte count falls to very low levels during the first week of postnatal life and remains so for the next five to seven weeks. During this period there is steady loss in body red cell and hemoglobin content. It was estimated, in the four infants shown, that during this period of sustained fall the red cells were being lost at the rate of 1.1 to 1.3% per day, as compared with the normal of 0.83% per day. These rates correspond to red cell survival times of 77 to 98 days, as compared with the normal of 100 to 120 days. This then, indicates that a slight element of increased rate of hemolysis does, indeed, exist in the premature infant. The survival times of 77 to 98 days are the maximum values which could exist, since they are based on the assumption that hematopoiesis has ceased completely. If the infant were also regenerating red cells to any significant degree, the survival time of the red cell population initially present would be even shorter in order to lead to a loss of total body red cells at a rate of 1.1 to 1.3% per day. The absence of any marked degree of regeneration is indicated by the persistently low reticulocyte levels during this time, as mentioned above. It may be noted that the two larger infants demonstrate shorter red cell survival times than the smaller babies. It is unlikely that this is actaully true, and the methods of obtaining these estimates are not sufficiently accurate to permit fine differentiation. We believe, however, that the evidence does indicate the existence of a slight hemolytic component in the premature infant. The latter, though, is by no means a major factor in the loss of body hemoglobin and red cell content. Indeed, even if red cells were being lost at the normal rate of 0.83% per day, the same trends would be evident and would further indicate inadequate hematopoiesis during this time. The rate of hemoglobin loss, it will be noted, was greater than that of the red cells and was estimated to be 1.2 to 1.43% per day. The same situation has been found in newborn infants by Gairdner,[58] who explained this on the basis that the red cells disappearing earliest are the ones which are larger than normal and have a higher hemoglobin content. The evidence for this lies in the fact that during the first three months of life the mean corpuscular volume and mean corpuscular hemoglobin decrease progressively in the full-term infant. We have found the same to hold true in premature infants. In addition, Wintrobe and Shumacker [61] have demonstrated that the size of the erythrocyte decreases progressively during fetal life. Thus, in agreement with the above authors, we believe that the largest and most hemoglobinized red cells present at birth are actually the oldest and the ones with the shortest life span.

During the second month of life, a spontaneous resumption of hematopoiesis occurs, as evidenced by a reticulocytosis and subsequent marked rise in total body hemoglobin. This stimulus to hemoglobin synthesis at this time apparently is of such magnitude that even fetal hemoglobin synthesis is temporarily resumed. As demonstrated in the figures, however, about 16 weeks were required before the hemoglobin mass present at birth was regained. It is thus apparent that the iron

derived from the initial destruction of hemoglobin remained available for reutilization when hemoglobin synthesis again began. In other words, for a period of 16 weeks more iron was available in the body stores than was utilized for hemoglobin synthesis. Added iron during this period, therefore, would not appear to be required. In addition, it will be noted from Figure 5 that while added iron given at 16 weeks permitted an uninterrupted gain in body hemoglobin, it did not increase the rate of hemoglobin formation over that which was taking place before iron was added. This circumstance would argue against the idea that medicinal iron is used more efficiently than that in body stores. If external sources of iron are not added soon after 16 weeks of life, however, hemoglobin synthesis slows markedly or stops. This fact indicates that the major iron reserve of the premature infant at birth lies in the hemoglobin mass itself and that probably relatively little storage iron exists in the liver or spleen. This concept is also held by Langley.[59]

In the studies of Merritt and Davidson,[9] it was found that the administration of iron soon after birth had very little effect in preventing the fall in hemoglobin concentration during the first two months of life. From the third month onward, however, the infants receiving iron demonstrated higher hemoglobin levels than the untreated ones. In a recent study, Reedy and co-workers[13] concluded that "the administration of iron during the first three months of life only has an unquestionably benign effect on the course of anemia in all premature groups." Examination of the latter authors' data, however, reveals that no difference exists between treated and untreated infants at 12 weeks of age; at 4 months of age a significant difference between treated and untreated infants is seen only in the group whose birth weight was 1,000 to 1,500 gm.; in the fifth and sixth months the treated infants demonstrated higher hemoglobin levels than the untreated in all weight groups. The fact that benefit was observed two months after cessation of iron therapy suggests that some of the iron which was administered during the first three months was absorbed and stored for later use. The question remains whether administration of iron during the first three months has any advantage over starting iron at 3 months of age. The data of Merritt and Davidson[9] indicate that infants who are treated after anemia develops lag behind those who are treated with iron from birth. In the present study (Fig. 5), however, it was shown that delay in iron administration until the 16th week did not result in any lag in hemoglobin synthesis. There appears to be rather general agreement that early administration of iron does little to modify the fall in hemoglobin concentration in the first two to three months of postnatal life. It also appears quite definite that iron should be given to the premature infant at some point before the fourth month of life. From our own studies we have been led to conclude that, even with a safety factor considered, added iron is not required before the third month of life.

Two questions of great interest now require consideration: 1. Do the changes observed in the premature infant differ from those in the full-term baby? 2. Are any basic physiologic mechanisms disclosed by the observed sequence of events? For at least partial answer to these questions we may turn to the recent studies by Gairdner, Marks, and Roscoe.‖ These authors made quantitative estimations of the blood changes in full-term infants during the first three months of life. The

‖ References 58 and 60.

blood volumes at various ages were derived from the data of Mollison and co-workers,[47] and total body hemoglobin and red cell content were calculated. In addition, serial studies of marrow activity and peripheral blood reticulocytosis were performed. Fetal and adult hemoglobins, however, were not determined. The findings in the above studies agree closely with those in the present investigation and indicate that the basic hematological changes which occur in the full-term and in the premature infant are almost identical. Thus, in the full-term infant the reticulocyte count falls to very low levels in the first nine days of life and remains so for about 60 days. Of great significance was the demonstration by Gairdner and co-workers [58] that within the first four days of life there occurs a profound drop in marrow erythroid cell count, thus giving further evidence for markedly diminished hematopoiesis during this period. As a result, a steady loss in total body hemoglobin and red cell content takes place during the first two months of life. At about 60 days of age, coincident with an increase in marrow erythroid activity and with peripheral blood reticulocytosis, the hemoglobin mass begins to rise and continues to increase. In these, the red cell survival times in the full-term infants were estimated to be within the normal range, in agreement with the findings of Mollison.[61]

Gairdner and co-workers [58] have proposed an intriguing and logical hypothesis explaining the observed sequence of changes. These authors believe that

> the fall in hemoglobin after birth is an expression of the increased oxygen saturation of the blood when lung replaces placenta as a source of oxygen. . . . that the changes in form and number of red cells after birth are due to variations in the erythropoietic activity of the marrow, and . . . that this activity is itself governed by the need to maintain the oxygen content of the blood at a constant level.

They point out that oxygen saturation of umbilical vein blood is about 65%. With the average cord blood hemoglobin of 17.6 gm. per 100 ml., this would give a value of 11.4 gm. per 100 ml. of oxyhemoglobin in the arterial blood of the fetus at the end of gestation. Within a few hours after birth, however, the arterial oxygen saturation reaches 95%. The authors believe that erythrogenesis thereupon stops until the hemoglobin level reaches 11 to 12 gm. per 100 ml. and then begins again and is sustained. The basic concept, therefore, is that erythropoietic activity is regulated by the arterial oxyhemoglobin level and that this, in the infant, is normally in the range of 11 to 12 gm. per 100 ml. Decreases below this level will induce increased hematopoietic activity, while elevations above this level will tend to decrease marrow activity. Evidence in favor of this hypothesis is presented in the studies of blood formation at high altitudes [62] and in studies of erythrogenesis in cyanotic heart disease.[59]

In the present study, increased erythropoietic activity began in the premature infant at five to seven weeks of postnatal life, i. e., at a somewhat earlier period than in the full-term infant. This activity may be explained by the fact that the hemoglobin concentration of the premature infant falls more rapidly than that of the full-term infant as a result of both the slight element of hemolysis and the more rapid rate of growth. Thus the hemoglobin concentration reaches the 11 to 12 gm. range at an earlier period in the premature than in the full-term. The results of the present study therefore lend support to the concept of Gairdner and co-workers.[58]

A final consideration of the present study relates to the need for transfusion in premature infants. It will be noted from the Figures that the resumption of hemoglobin formation has already begun while the hemoglobin concentration in the peripheral blood is still falling. Thus, at the time when transfusion is usually being considered, processes of recovery are already under way. Birkhill and co-workers [63] have shown that the administration of blood to normal persons will retard hematopoiesis until the normal hemoglobin level is regained. In recent studies in our own laboratory,[64] we have found that even in children with chronic anemias the administration of blood will decrease the level of endogenous hematopoietic activity to a degree which is proportional to the amount of blood given. Thus, in premature infants, it is quite likely that indiscriminate use of transfusion may retard the spontaneous process of recovery. It should be emphasized, however, that conditions known to depress hematopoiesis, such as infection and other debilitating disorders, may necessitate the use of transfusion therapy.

SUMMARY AND CONCLUSIONS

Quantitative data relating to blood formation and blood destruction in premature infants are presented.

The basic physiologic alteration underlying the development of the anemia of prematurity appears to be a marked decrease in hematopoietic activity in the early neonatal period. This, when coupled with a slight decrease in erythrocyte longevity, leads to a pronounced fall in total body red cell and hemoglobin content.

Spontaneous recovery begins at 5 to 7 weeks of age and is heralded by a reticulocytosis.

During the first three to four months of life, more iron exists in the body than is utilized for hemoglobin synthesis. During this period, therefore, prophylactic administration of iron does not appear indicated. After the age of 3 to 4 months, however, added iron is required to maintain optimal rates of hemoglobin production.

The changes in premature and full-term infants are compared, and theories concerning the physiologic bases for these changes are presented.

The need for transfusion in the treatment of the anemia of prematurity is discussed.

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DISAPPEARANCE AND MIGRATION OF EPILEPTIC FOCI IN CHILDHOOD

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IF THE electroencephalographic and clinical features of epilepsy are viewed over a period long enough to allow maturational changes to become evident, certain phenomena appear that are as regular, predictable, and important as are more obvious short-time manifestations. This and previous studies [1] show that the type of seizure and the location of the focus (when one is present) are largely determined by the age of the patient and the maturational state of his brain.

In order to obtain correlations and consistent relationships such as are reported here, it is necessary that electroencephalographic recordings be made in the waking and sleeping states. This statement may sound dogmatic, but it is supported by comparison of recordings awake and asleep in many thousands of cases [1] and it is basic to the present discussion. To put the matter figuratively, sleep takes the blanket off the brain and reveals seizure discharges and underlying disorder that rarely appear in the waking state.

GENERALIZED SEIZURE ACTIVITY

The brain of an infant tends to react to a variety of insults with generalized and continuous disorder, but at later ages this reaction becomes at first temporally limited and later spatially confined. For example, in the first year of life generalized continuous electroencephalographic abnormality is common; when severe, it appears as extremely high-voltage almost continuous slow waves interspersed with single spikes and multiple spikes. This pattern has been called hypsarrhythmia (mountainous arrhythmia) [1]; it indicates the most malignant form of epilepsy.[2] In the second to fifth years, a generalized but interrupted (i. e., temporally limited) disturbance is common, consisting of generalized slow spikes ("sharp waves") alternating with slow waves. This generalized pattern repeating approximately twice a second indicates petit mal variant, the next most malignant form of epilepsy. In the 6th to 12th years, generalized three-per-second spike and wave discharges are common; they indicate petit mal, a relatively benign form of epilepsy. As has been emphasized, all these types of disorder are generalized. Although they are more or less specific for certain ages, one does not tend to be transformed into another with increasing age; for example, hypsarrhythmia does not commonly change into petit mal variant and petit mal variant almost never changes into petit mal.

At the time of this study, Research Fellow of the National Institutes of Neurological Diseases and Blindness (Dr. Gillen).

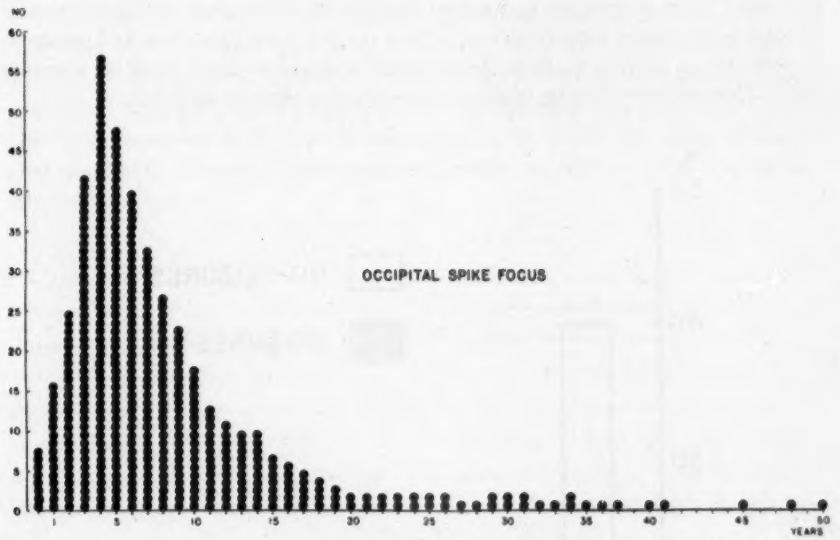

Fig. 1.—Age distribution of 439 patients with a focus of spike seizure activity in one or both occipital lobes and no other foci.

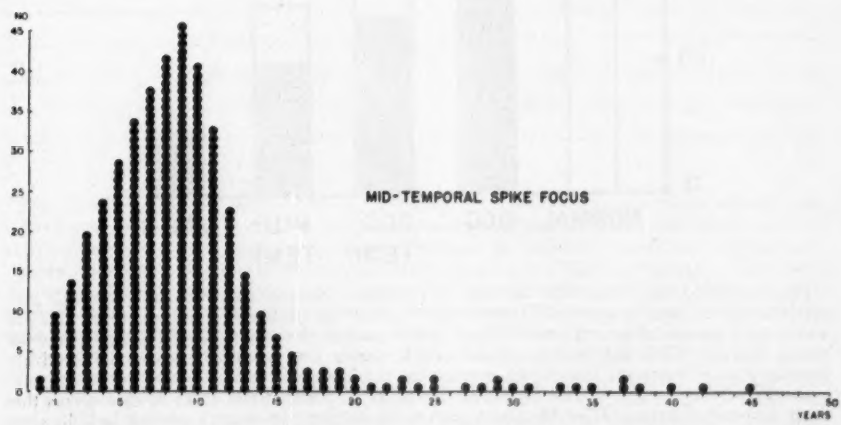

Fig. 2.—Age distribution of 436 patients with a focus of spike seizure activity in one or both midtemporal areas and no other foci.

FOCAL SEIZURE ACTIVITY

After adolescence, generalized seizure activity becomes rarer. A high percentage of patients who in early childhood had generalized disorder later develop multiple foci. New cases of epilepsy that appear during late adolescence are likely to have 14- and 6-per-second positive spikes.[1] These occur during light sleep and presumably indicate an epileptic focus in the thalamus or hypothalamus. Anterior temporal spikes are commonest among persons whose seizures begin in adult life.

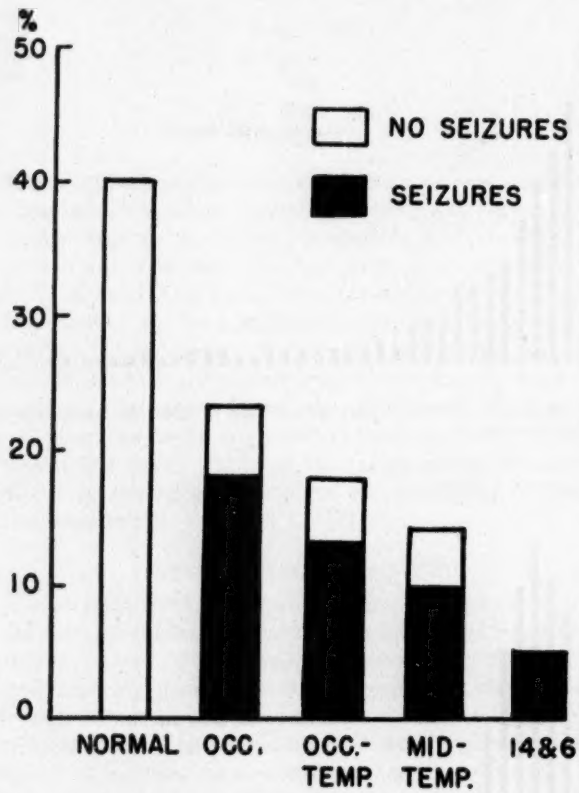

Fig. 3.—Follow-up study after the age of 9 years of 49 patients who had previously had occipital foci of seizure activity. Columns show percentage incidence of certain types of EEG with (black portion of column) and without (white portion of column) clinical seizures. *Normal* means that the EEG had become normal; *OCC.* means that occipital focus of spike seizure activity was still present; *Occ.-Temp.* means that the focus had moved to the occipitotemporal area; *Med-Temp.* means that the focus had moved to the midtemporal area; *14 & 6* means that other foci had disappeared but 14- and 6-per-second positive spikes were present in light sleep (these are presumptive evidence of an epileptic focus in the thalamus or hypothalamus).

From the foregoing it is apparent that generalized epileptic disorder is more or less characteristic of infants and young children, whereas focal epilepsy is characteristic of late adolescents and adults. However, epileptic foci occur at all ages and are by no means rare, even in the youngest age groups. The characteristic focus of

the very young is an occipital focus.[1] It is particularly common in children 4 years of age (Fig. 1). Older children are more likely to have a focus in the midtemporal area; such foci are commonest in the ninth year (Fig. 2).

Although our previous studies [1] showed that the epileptic process takes different forms and selects different brain areas at different ages, the cross sectional data on which these studies were based did not provide an answer to the following crucial questions: What becomes of an occipital or temporal focus as a child grows older? Does it disappear or shift to some other part of the brain? In order to answer these questions, follow-up studies were undertaken on patients with occipital and temporal lobe foci.

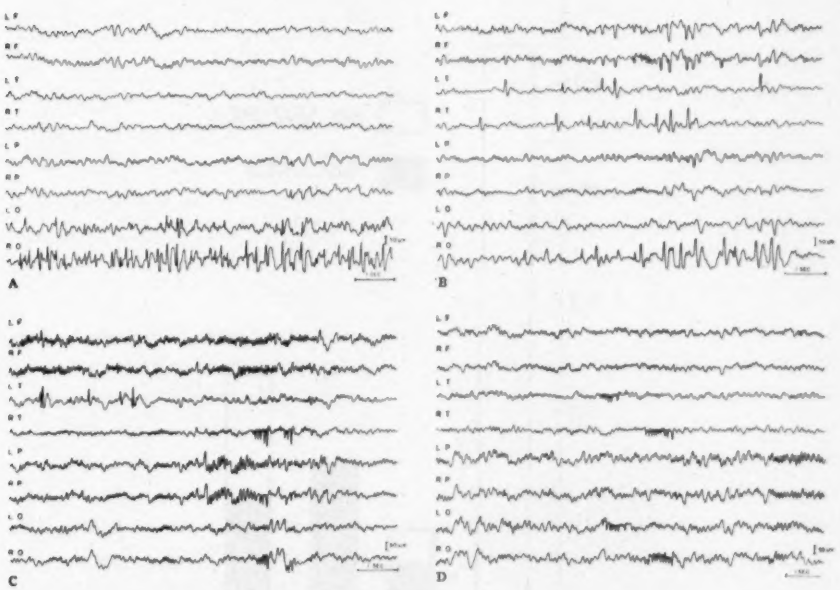

Fig. 4.—*A*, boy, aged 7 years, with four episodes of prolonged unconsciousness without convulsive movements but with choking, gagging, vomiting, and cyanosis. The first attack occurred at one year of age; the second with measles at 2 years; the third at 6 years, and the fourth at 7 years. Strabismus, left eye turned in. On diphenylhydantoin (Dilantin) therapy. EEG: focus of sharp spikes and slow waves in the right occipital area, showing also in the left occipital area. *B*, same patient, 8 years of age. Since the previous EEG, one choking spell and three tonic-clonic convulsions. On diphenylhydantoin therapy. EEG: fewer spike seizure discharges in the right occipital area, none in the left; the spikes are slower than previously; however, independent foci of spike seizure activity are now evident in both midtemporal areas spreading as a positive spike to both frontal areas. *C*, same patient at 10 years of age. No further seizures, but complained of dizzy spells and headaches. Still on diphenylhydantoin therapy. EEG: light sleep. The negative spike foci in the right occipital and the right temporal areas have disappeared. However, the negative spike focus in the left midtemporal area persists and 14-per-second positive spikes are now evident in the right hemisphere (presumptive evidence of a focus of epileptic disorder in the thalamus or hypothalamus). *D*, same patient at 12 years of age. No more clinically evident seizures or dizzy spells, but patient complained of headaches. Still on diphenylhydantoin therapy. EEG: light sleep. Fourteen-per-second positive spikes in the right and left hemisphere (suggesting epileptic foci in the thalamus or hypothalamus). The spike discharges are of lower voltage than in the previous recording.

OCCIPITAL LOBE FOCI

Forty-five children who were known to have had occipital foci of seizure activity were restudied after they had reached 9 years of age. In 40% of these cases the focus had disappeared and the electroencephalogram had become entirely normal; all of these patients were free from clinical seizures. Twenty-three per cent still had an occipital-lobe focus, and of these about one-quarter were seizure-free. In 18%, the occipital spike focus had disappeared and had been replaced by an occipito-temporal focus; about one-quarter of these were seizure-free. In 14%, the focus had

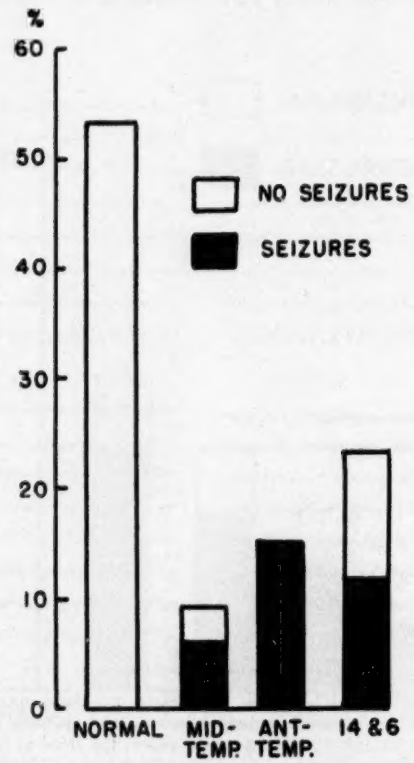

Fig. 5.—Follow-up study after the age of 15 years of 98 patients who had previously had a midtemporal focus of seizure activity. Columns show percentage incidence of certain types of EEG with (black portion of column) and without (white portion of column) clinical seizures. *Normal* means that the EEG had become normal; *Mid-Temp.* means a midtemporal focus of seizure activity was still present; *Ant-Temp.* means focus had now shifted to the anterior temporal area; *14 & 6* means other foci had disappeared but 14- and 6-per-second positive spikes were present in light sleep (these are presumptive evidence of epileptic focus in the thalamus or hypothalamus).

shifted to the midtemporal area, and of these about one-third were seizure-free. Five per cent had developed 14- and 6-per-second positive spikes (presumptive evidence of epileptic disorder in the thalamus or hypothalamus), and approximately one-third of these were seizure-free. These facts are presented graphically in Figure 3, and an illustrative case is shown in Figure 4.

None of the 45 patients who had had an occipital focus developed diffuse seizure activity or an anterior temporal focus; however, such cases probably occur and in a large series would be encountered.

MIDTEMPORAL LOBE FOCI

Ninety-eight patients who were known to have had a midtemporal focus of seizure activity were restudied after the age of 15 years. In 53%, the EEG had become normal; all of these patients were seizure-free. Nine per cent still had their temporal-lobe focus, and one-third of these were seizure-free. In 15%, the focus had shifted to the anterior temporal area; none of these patients were seizure-free. In

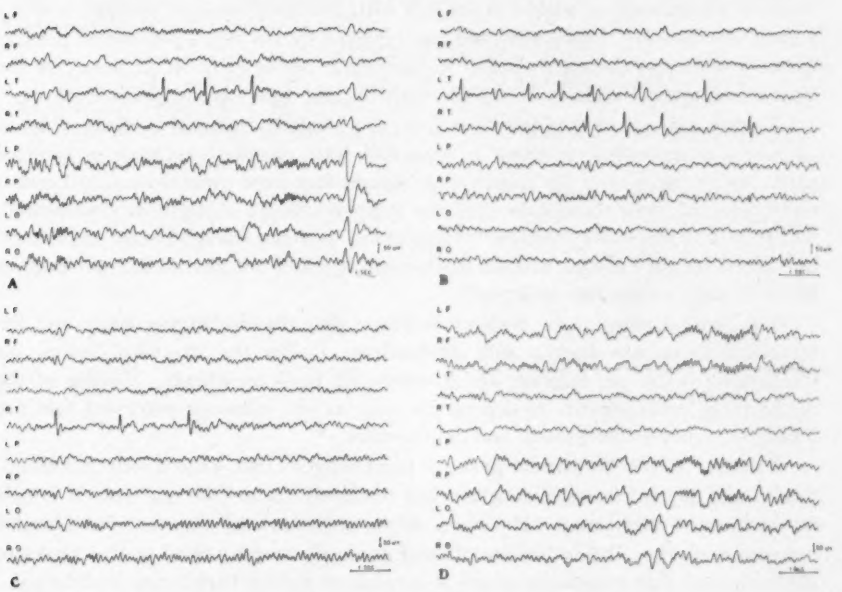

Fig. 6.—*A*, boy, aged 7 years. Nightly seizures consisting of convulsive movement of the right face and right arm without loss of consciousness, continuing for several hours; unable to talk after the attack; receiving special training for speech defect. EEG: light sleep. Focus of high-voltage spike seizure activity in the left temporal area. *B*, same patient at 9 years of age. Still having the same type of seizure, but the attacks sometimes involve the right side and sometimes the left. EEG: independent high-voltage spike seizure activity in the right as well as left midtemporal areas. *C*, same patient at 11 years of age. No seizures for one year. On diphenylhydantoin therapy. EEG: spike seizure discharges continue in the right midtemporal area but have disappeared in the left. *D*, same patient at 13 years of age. No seizures since 10 years of age; speech completely normal; off medication for one year. EEG: moderately deep sleep. Normal. On repeated examination (at ages 14, 15, 16, and 17 years) this patient has continued to have a normal EEG awake and asleep. He has remained free of clinical seizures, has done well in his studies, is well adjusted socially, and has no handicaps or defects.

23%, the midtemporal focus was replaced by 14- and 6-per-second positive spikes; half of these patients were seizure-free. These statistics are presented graphically in Figure 5, and an illustrative case is shown in Figure 6.

COMMENT

The present findings indicate that with increasing age discharging lesions in the occipital lobes, which are common in infants, tend to heal or to migrate forward into the temporal areas. Midtemporal discharging lesions, which are common in children, tend to heal before adolescence or else to migrate downward into the thalamus or hypothalamus or forward into the anterior temporal lobe. Thus, with increasing age focal seizure activity tends to disappear or to move into the site that is characteristic for seizure activity at the age which the patient has attained.

When the focus migrates to another area, the clinical seizure commonly changes to accord with the symptomatology usually associated with seizure activity in that area. For example, when the focus moved from an occipital to a mid-temporal-lobe, the patient commonly developed clinical seizures restricted to one side of the face, which is a usual type of seizure in patients with mid-temporal-lobe epilepsy.[1] When a midtemporal focus disappeared and was replaced by 14- and 6-per-second positive spikes, the patient commonly began to have dizzy spells (Fig. 4*C*); these are the most usual types of seizures in patients with 14- and 6-per-second positive spikes.

Twenty per cent of the patients in these two series had clinical evidence of brain damage ("symptomatic epilepsy"); they had been classified as cases of cerebral palsy. In all these cases the neurological defects that were present remained essentially constant, even though the epileptic symptomatology changed or disappeared. The foci of patients with so-called "symptomatic" epilepsy changed in the same manner as the foci of patients without known etiology and without clinical evidence of brain damage (idiopathic epilepsy?).

The general sense of the evidence indicates that the discharging lesion and the structural lesion are distinct and independent. Unlike the structural lesion, the discharging lesion can migrate, and it commonly heals completely. Healing of the discharging lesion appears to depend on some as yet unknown processes that are intimately related with growth and development.

Experience with the present group of cases suggests that when a focus has disappeared and the electroencephalogram has remained normal for one year it is safe to discontinue medication. However, when phenobarbital or other barbiturates are employed, they should be discontinued gradually over a period of two weeks to avoid flare-up that sometimes occurs as a result of sudden barbiturate withdrawal.

SUMMARY AND CONCLUSIONS

Follow-up studies were carried out on 45 children who had passed their ninth birthday and who before the age of 9 years had had an occipital-lobe focus of seizure activity. Similar follow-up studies were carried out on 98 patients who had passed their 15th birthday and who before the age of 15 had had a mid-temporal-lobe focus. All the original electroencephalographic studies on these cases were made in both the waking and sleeping states, and seizure foci had been found only in the areas specified. At the time of the follow-up studies, electroencephalographic recordings were again obtained in both the waking and sleeping states, for it was recognized that in a high percentage of cases epileptic disorder does not appear in the waking state.

Of patients who had had occipital-lobe epilepsy, 48% no longer had any evidence of disorder, i. e., their EEG's had entirely normalized after the age of 9 years. Of

those who had had mid-temporal-lobe epilepsy, 50% no longer had any evidence of disorder, i. e., their EEG's had entirely normalized after the age of 15 years. Clinical seizures had ceased before the electroencephalogram became normal.

Present experience suggests that it is wise to continue anticonvulsant medication until one year after the last seizure in cases in which a previously abnormal EEG has become normal awake and asleep. Normalization of the EEG is evidence of a recovery process that probably has carried the patient out of danger of further seizures. In order to play doubly safe, however, medication can be continued for another year; a second normal electroencephalogram awake and asleep at the end of that time indicates that no relapse has occurred and gives added assurance that medication can be discontinued without a recurrence of seizures.

Unless a tumor, abscess, depressed fracture, or other lesion which requires surgery is present, a neurosurgical attack on occipital and midtemporal foci in children is contraindicated.

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CASE REPORTS OF PROGRESSIVE INFANTILE MUSCULAR ATROPHY (WERDNIG-HOFFMANN) IN FRATERNAL TWINS

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IT HAS been pointed out by investigators that progressive infantile muscular atrophy as first described by Werdnig and Hoffmann has distinct hereditary-familial tendencies. Up to the time of a report by Brandt,[2] 200 cases occurring in 120 families had been reported. Review of the role of heredity in disease [3] reveals that the same developmental anomaly can occur in more than one child of a family and often in several generations. In anomalies in general, the same malformation may occur in both identical twins, but it is unusual for fraternal twins to be affected by the same malformation.[1] Also, mechanisms which are dependent on heredity in congenital defects are apparently dependent on recessive rather than dominant sex characteristics.

The relationship of infantile progressive muscular atrophy to that of Oppenheim's disease, or amyotonia congenita, is not disputed by most authorities. The fact that these conditions may be closely related and be present in the same family is brought out by a study of these cases.

A brief summary of the family history revealed that both parents were of Norwegian extraction and that all four grandparents were of Norwegian birth.

One sibling, born in June, 1951, weighed 7½ lb. (3,400 gm.) at birth and was noted to have a generalized weakness of the body approximately three weeks after birth which began in the legs and progressed to the trunk, chest, and upper extremities, and then to the muscles of the neck and head, with inability to swallow. This first sibling died at the age of 7½ months. The diagnosis of amyotonia congenita, or Oppenheim's disease, was made at the Mayo Clinic, Rochester, Minn., in August, 1951.*

REPORT OF CASES

Since the courses of the illness in these twins were parallel, a combined summary is given.

These 7½-month-old white twin girls, of Norwegian ancestry, were admitted to Hahnemann Hospital to the service of Dr. Carl C. Fischer because of recurrent upper respiratory infections, dyspnea, and dysphagia. History of these infants revealed that they were delivered after a full-term pregnancy on Oct. 26, 1952, the mother's second pregnancy, which was carried to term, although cholecystectomy and appendectomy were performed on the mother at three months' gestation. Delivery of these children was uneventful, and at birth it was noted that they were not identical. Examination of the placenta revealed a double, though fused, placenta. One child was dark-haired at birth, while the other was light-haired. The firstborn of the twins weighed 6 lb. 14½ oz. (3,130 gm.), and the secondborn, delivered 1 hour and 35 minutes later, weighed 5 lb. 14½ oz. (2,680 gm.). Delivery occurred approximately one week prior to the estimated

From the Division of Pediatrics, Hahnemann Medical College and Hospital of Philadelphia.

* Keith, H. M.: Personal communication to the author, October, 1953.

date of delivery. The neonatal period was uneventful except for occasional short periods of cyanosis in the secondborn for the first week. Both infants developed rapidly, having had good sucking reflexes at birth, and both were able to raise their heads well, were able to roll over, and had begun to sit up prior to the onset of the present illness, which began at the age of 5 months (March, 1953). The mother noted that these children were unable to raise their legs off the bed, and soon after they were unable to roll over, as they had previously. By the age of 6 months, they had lost some sucking reflex, and dysphagia appeared. The symptoms grew progressively worse, with additional symptoms of difficulty in clearing the throat. This condition was quickly followed by an episode of pneumonia, which was controlled with antibiotic therapy. In quick order, acute stomatitis and recurrent "Streptococcus sore throats" developed. By 7 months of age, they had had increasing difficulty with swallowing and control of secretions of nose and throat. Their history to date of admission indicated a progressively downhill course, and on admission to this hospital they exhibited the following features:

Both infants showed marked evidence of loss of weight, weighing 14 lb. (6,350 gm.) and 13 lb. 4 oz. (6,010 gm.), respectively, and exhibited dyspnea and stertorous breathing. Neither infant could move her legs, even after stimulation. Their chests showed evidence of deformity in the lateral projection and some degree of pigeon breast, with some retraction of interspaces on inspiration. There was an accumulation of mucoid secretion in the oropharynx in both twins, which seemed to redevelop soon after aspiration.

A neurological examination revealed the absence of deep and superficial reflexes in both legs of each twin. All muscles were flaccid and atrophic in both legs. There were diminished tendon reflexes in both upper extremities and strength sufficient only to allow them to raise a small light toy. The upper cranial nerves appeared intact except for diminished palatal reflexes. There was a marked laxity of the joints of the body, allowing these children to fall backward or forward without control.

Laboratory Data.—X-ray of the chest of the firstborn revealed consolidation of the right upper lobe. There was minimal compensatory emphysema noted on this examination. X-ray of the chest of the secondborn showed evidence of a consolidating process involving the right middle lobe. On fluoroscopy, both twins were noted to breathe chiefly with diaphragmatic control, rather than through intercostal muscular control.

Urinalysis was noncontributory. Hematology failed to show other than evidence of hypochromia, poikilocytosis, and a moderate anisocytosis. ECG in each infant was normal. Estimations of plasma tryptophan and methionine levels were normal.

Biopsy of the gastrocnemius muscle of both infants showed evidence of diffuse atrophy compatible with a diagnosis of muscular atrophy.

Neurological consultation confirmed the presence of a lower motor neuron disease affecting the nuclei of the lower brain stem and the locomotor neurons in the spinal cord. A finding of infantile muscular atrophy (Werdnig-Hoffmann type) was confirmed. Short trials of therapy with neostigmine (Prostigmin) in one infant and corticotropin (ACTH) in the other were instituted, but with little effect in either case.

After nine days' stay, these infants were discharged to their home in a far-western state, where their death was reported in August, 1953, approximately one month after discharge from this hospital.

SUMMARY

Two cases of infantile muscular atrophy (Werdnig-Hoffmann) occurring in fraternal twins are reported. The first, and only other, sibling of this family was affected similarly with Oppenheim's disease, or amyotonia congenita.

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Case Reports

PERIPHERAL VASCULAR DISEASE WITH GANGRENE AND HEMIATROPHY IN A CHILD OF THREE YEARS

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PERIPHERAL vascular disease in the young child is rare. Most case reports feature gangrene of the limbs in neonates, ascribed to a variety of causes. An instance is described by Brown and Smith [1] where gangrene of the hand in a newborn infant was found to be due to thrombosis of the subclavian artery in the absence of congenital heart disease. Stadler [2] records an unusual case of neonatal symmetrical gangrene of the feet, with ultimate complete recession. The femoral, popliteal, and dorsalis pedis arteries were apparently normally palpable, but the author considered a congenital lesion as a possible cause.

Stokes and Shumacker [3] review sudden gangrene in infants and report four cases of their own, only one of which was a neonate. It was their observation that the condition occurred in chronically ill, often dehydrated, children. One of their cases had undergone a period of hypotension; in another, femoral venous puncture had preceded gangrene of the corresponding foot.

Obliterative peripheral vascular disease in children has received scant attention in the standard texts. Thus Lewis [4] does not mention the condition of thromboangiitis obliterans in children, and Wright [5] states that this condition is rare under the age of 15 years and gives no further details. Kramer [6] does not describe cases of obliterative vascular disease at this age other than those with an infective or other obvious cause. Arteriosclerosis in young age groups has been reported by Lipman and co-workers.[7] In these cases the symptomatology was primarily cardiac, the peripheral vessels being clinically unaffected.

REPORT OF A CASE

A white girl, aged 3 years 9 months, of German-Norwegian stock, was the product of a normal pregnancy and delivery. Condition at birth was satisfactory, and she was perfectly well until the age of one year. At that time it was noted that the fingers of the right hand and corresponding toes were dusky and "reddish-blue." This appearance was accentuated by cold. The mother thought that the right hand was smaller than the left. By the age of 15 months, when the patient began walking, a limp of the right leg was noted, and this limb was found to be shorter than the left. X-rays of the spine were taken and were said to show no abnormality. No acute or febrile illness had occurred, and she had never been dehydrated.

Since the age of 2 years, the child had complained of pain in the right foot at night; this was usually of short duration and moderate severity. The fingers and toes on the right had always been noticeably cool. Seven months before admission to this hospital she had stubbed her right foot; the middle toenail of this foot had always been "curled up," but this time the toe became more discolored, and an infection developed. The nail was removed, but the wound

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never completely healed. Two weeks before admission, the toe became swollen, and a purulent discharge appeared. The family history was irrelevant. The child lived on a farm, and some of the rye had "blight." She had never practiced pica, and did not eat raw grains. The family did not bake their own bread.

Measurements of Leg Size

	Right, Cm.	Left, Cm.
Acromion-finger tip	39.5	42.0
Anterior superior spine-medial malleolus	46.5	49.0
Circumference of calf	19.0	20.5
Circumference of thigh	26.0	28.0

Metatarsal size (x-ray measurement) L > R by 6-8 mm.

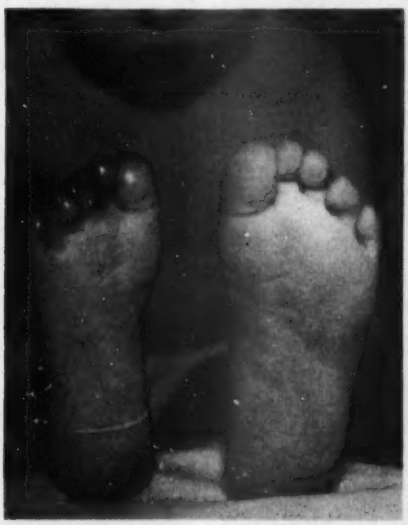

Fig. 1.—Both Feet. The color change and gangrene of the toe are visible in the right foot. The difference in size as compared with the left is also demonstrated.

Physical Examination.—The girl weighed 32 lb. (14.5 kg.), and her height was 38 in. (96.5 cm.). There was obvious difference in the growth of the right and left upper and lower limbs (Table and Fig. 1). She walked with a limp of the right leg. Her right hand, fingers, and thumb were dusky red in appearance and cool in comparison with the corresponding left ones. Raynaud's phenomenon was absent. The right toes and the anterior part of the dorsum of the foot were dusky. The skin felt cool, and the middle toe was edematous. The nailbed sloughed, and a black area of gangrene presented at the tip of the toe, which was painful to touch (Fig. 1). Dependent rubor deepening to cyanosis was present; pallor appeared on raising the leg. There was no impairment of sensation in the foot or leg. The right radial and brachial pulsations were absent, as were the popliteal and pedal impulses. The right femoral pulse was weak. The left-side arteries were apparently normal. Blood pressure (left arm), 105/75. Heart size and sounds were clinically normal. Other systems were within normal limits.

Laboratory Investigations.—Urinalysis and blood cell count (with differential) were normal. Blood sugar (fasting), 73 mg. per 100 cc.; N. P. N., 31 mg. per 100 cc.; serology, negative.

Spinal tap, pressure, and constituents were normal. X-rays of the chest and skull were normal. In the long bones the difference in size noted clinically was confirmed. The epiphyses were normal, as was bone density. No vascular calcification was observed.

Pneumoencephalogram showed incomplete ventricular filling, but no shift was present. The cortical pattern was essentially normal, as were the basal cisterns.

Femoral arteriography (Figs. 2 and 3) was performed on both sides. The caliber of the arteries visualized on the right (affected) side, was narrowed, and the luminal contour, irregular. Only one of the major arteries of the lower leg was visualized, the posterior tibial. No vascular filling was seen in the foot. On the left (clinically unaffected) side, opacification of the vessels extended to the foot. Caliber of the vessels was distinctly larger than on the right. The femoral artery had a smooth lumen; in the branches slight irregular variations in caliber were seen, which might be due to intrinsic vascular disease.

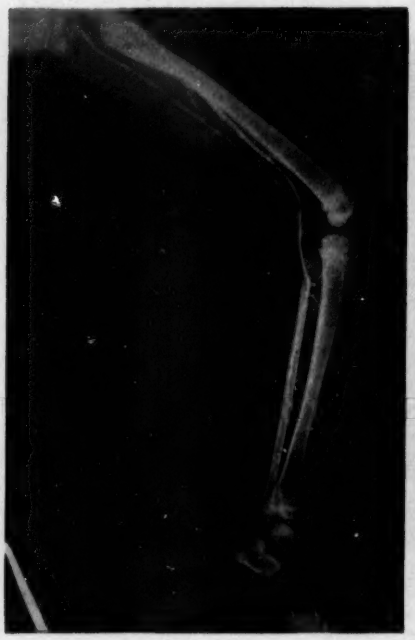

Fig. 2.—Right femoral arteriogram. The irregularity in the lumen of the femoral artery is shown. The anterior tibial artery and foot vessels do not fill.

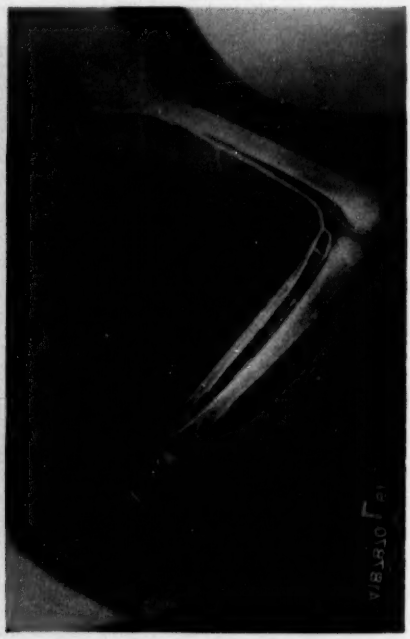

Fig. 3.—Left femoral arteriogram. The femoral lumen appears normal (cf. Fig. 2). The anterior and posterior tibial arteries are present, and opacification extends into the foot. Slight irregularities of caliber are seen in the upper part of the tibial arteries.

The skin temperature was assessed in a constant-temperature room by means of a thermocouple. A 4 degree (F.) difference between the great toes existed at rest; a similar though less marked difference extended to the midthigh level. A temperature difference between the two upper legs also was present.

Reflex vasodilation was induced by immersing the left hand, arm, foot, and leg in warm water. The temperature in the affected foot could be raised by 2 degrees (F.). Sympathetic block on the right side gave similar results.

Progress.—The child was observed for two weeks, during which time the entire terminal phalanx of the right middle toe sloughed. The color changes in the skin became more marked.

Treatment.—Right lumbar sympathectomy was performed. The child made an uneventful recovery. Postoperative assessment of skin temperature (hallux) showed an increase of 2 degrees above the preoperative level. The difference in the temperature between the two great toes had fallen to 2 degrees (4 degrees preoperatively).

The cellulitis accompanying the gangrene was now well controlled, and early granulations covered the affected area.

COMMENT

The causes of obliterative peripheral vascular disease have been given by Wright.[8] In this case vasoconstrictive syndrome may be largely ignored in view of the absence of peripheral pulses and arteriographic findings. Intoxication by ergot was considered, but again the distribution and the lack of other symptoms or definite history of ingestion of rye products appeared to exclude this. Syphilitic affection of the vessels is rare in this age group and is negated by the result of serologic studies.

Periarteritis nodosa was considered briefly, but the bizarre history was absent, and there was no sign of multiple organ involvement; fever and eosinophilia were absent. No skin lesion of lupus erythematosus or scleroderma was present. As noted above, arteriosclerosis has been reported in young children, but the symptoms were primarily due to the coronary involvement. Prior and Bergstrom [8] report two cases with calcific changes in the arteries. In one there was peripheral gangrene. It is not thought that this case is one of arteriosclerotic vascular disease as seen in adults. The occurrence of thromboangiitis obliterans in the pediatric age group is rare indeed, but the arteriographic evidence in this case appears to clinch the diagnosis.

Much has been written concerning thromboangiitis obliterans in adults. It is a disease originally said to be found principally in Jews of Eastern Europe, but the disease has been found in many races.[5] It is often associated with heavy cigarette smoking. The sex incidence is predominantly male,[9] though many cases in females have been reported.[5] A review of the literature emphasizes the rarity of the condition in children. A case occurring in a 2-year-old Jewish boy is recorded by Cahill.[10] Here, the lesion was of acute onset, and the diagnosis was made by examination of the amputated limb. No details are given of the arterial pulsations; the case was thought clinically to be embolic in origin, being accompanied by fever and leucocytosis.

Buerger's [9] original criteria for the diagnosis of thromboangiitis obliterans were pain at rest (commonly at night), intermittent claudication, color, and trophic changes. He also noted the frequent occurrence of phlebitis, though Wright [8] states that this occurs in only 50% of cases. Absence of arterial pulsations, positional variation of skin color, and temperature difference are accepted signs.

Most of these phenomena, with the exception of phlebitis, were present in the case presented. It is difficult in this age group to know if true claudication pain is present, but a noteworthy point in the history was the occurrence of the intermittent limp long before the onset of the overt infection of the foot.

On the basis of the evidence presented it is considered that this is a case of thromboangiitis obliterans. The hemiatrophy associated with the vascular difficulty may be of primary origin, though the face was unaffected, and a search of the literature shows no report of a case of hemiatrophy with associated vascular disease. It is considered that the atrophy may be due to impaired local blood supply in the

growing period. Messent and co-workers [11] have noted that clinical considerations are probably most reliable in assessing the surgical treatment of vascular disease. Therefore the results of reflex heating and of sympathetic block were accepted with reserve. The increase in temperature and improved local condition appear, however, to have justified sympathectomy in this case.

The prognosis in this case, as in all cases of peripheral vascular disease, is guarded, especially in view of suggestive early changes in the arteriogram of the apparently normal side.

SUMMARY

A case of obliterative peripheral vascular disease in a 3½-year-old girl is presented. The lesion, present for at least two and one-half years, was considered to be thromboangiitis obliterans. Gangrene of a toe had occurred, and the affected limbs were smaller than the normal contralaterals. The age at onset, site, and clinical features are unusual.

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NEONATAL GLOMERULONEPHRITIS AND NEPHROTIC SYNDROME IN A 1,320-GM. PREMATURELY BORN INFANT

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ALTHOUGH the nephrotic syndrome in glomerulonephritis is common in early childhood, its occurrence in the neonatal period is extremely rare and, so far as we have been able to determine, has not been described in the literature in the newly born premature infant.

In 1930, Mitchell [1] reviewed the literature on congenital nephritis and nephritis in the newborn infant and found a few cases in the foreign literature before or at the turn of the century.

Lapage,[2] in 1932, reported a case of "hemorrhagic nephritis" in an 11-day-old full-term boy. The autopsy did not show glomerulonephritis. Conrad,[3] in 1938, reported three cases of neonatal nephritis in full-term infants, with one death. No autopsy was obtained, and therefore the type of nephritis was not determined.

Montagna and Ausberg,[4] in 1942, reported the case of a full-term boy dying on the 18th day with a clinical diagnosis of glomerulonephritis. There was no autopsy. The cause of the nephritis was attributed to toxins absorbed from the tuberculous mother.

Thompson,[5] in 1951, reported glomerulonephritis during the neonatal period in a full-term infant, which he considered secondary to circulating toxins from the mother, who had a pharyngitis during pregnancy.

Potter [6] says that "glomerulonephritis is unknown in the newborn and rarely a few partially hyalinized glomeruli can be found in the parenchyma of otherwise normal kidneys; they result from a malformation of the glomerular tuft and are unrelated to an infectious process."

Goettsch,* in a recent personal communication, states that her youngest patient was a full-term newborn who lived to be 4 months old. Autopsy revealed a very mild intracapillary glomerulonephritis.

Eiben and associates [7] currently reported a case of the nephrotic syndrome in a neonatal premature infant weighing 2,110 gm. at birth and dying on the 103d hospital day. Laboratory and clinical findings were considered compatible with the diagnosis of pure lipoid nephrosis.

Collins [8] recently reported chronic and subacute glomerulonephritis in a full-term infant, diagnosed at autopsy. Death occurred 90 hours after birth. The pathogenesis was not explained.

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* Goettsch, E.: Personal communication to the authors.

REPORT OF A CASE

C. F., a white boy, was born prematurely at home on Dec. 4, 1952, of a healthy 27-year-old mother. The birth weight was 1,320 gm. The mother had received no prenatal care during pregnancy but stated that she had been in good health. There were four previous full-term pregnancies and all children were living and well. The infant was delivered with a cephalic presentation and labor lasted three and one-third hours. It was stated that the cord was around the neck, and a tracheal catheter had been used immediately after delivery. There was no known factor to account for premature labor, but on the previous day the house had been painted and the fumes had nauseated the mother. The mother's blood was Rh positive and the Kahn test was negative.

On arrival at the Sarah Morris Hospital Premature Nursery two hours after birth, the baby was in poor condition. Examination showed pallor and slight cyanosis with slight infrasternal retractions; the cry was weak, and the infant appeared apathetic. There was moderate separation of all sutures. There were no other significant findings. Because of tracheal catheterization and the possibility of ensuing pneumonia, penicillin (75,000 units daily for three days) was administered prophylactically. Oxygen was administered in a Hess incubator.

The infant's condition gradually improved, although hypertonicity and rigidity of both knees and hips were noted. Roentgenograms suggested a subluxation of the left hip. However, the physical findings gradually cleared spontaneously and eventually there was no limitation of motion.

On the sixth day, the patient was doing well and oxygen was discontinued. Feedings were administered without difficulty from a small bottle for premature infants. On the ninth day, slight pitting edema of the face was noted. The hemoglobin was 15.8 gm. per 100 cc.; red blood cells, 4,430,000; white blood cells, 9,500, with a differential count of 54% segmented polymorphonuclears, 6% eosinophiles, 31% lymphocytes and 9% monocytes. Edema was rapidly progressive in the next few days and involved subsequently the eyelids, neck, right lower arm, and lumbosacral area, and finally became generalized. A transfusion of 35 cc. of whole blood was given on the 18th day, without any remarkable change in the infant's appearance. The weight had increased from 1,320 gm. on the 7th day to 1,500 gm. on the 17th day. On the 22d day the baby received 30 cc. of irradiated pooled human serum intravenously. Blood drawn at this time revealed total proteins 3.8 gm. per 100 cc., with albumin 0.6 gm. and globulin 2.3 gm. per 100 cc., serum cholesterol 321 mg., with 155 mg. esterified, and urea nitrogen 14.5 mg. per 100 cc. The blood serum was milky in appearance. Urinalysis done a few days previously revealed 3 to 4+ albumin, a few red and white blood cells, and fine and coarse granular casts. Blood pressure determinations were attempted, without success.

On the 23d day, small pustules were noted on the lower abdomen and several large abscesses on the lower back. These were incised, and pus was cultured. A blood culture taken at this time revealed a coagulase-negative hemolytic Staphylococcus albus, probably a contaminant. A coagulase-positive Staphylococcus aureus was recovered from the pus. Penicillin and streptomycin were administered intramuscularly daily. In spite of the abscesses and persistent edema, the general condition appeared fairly good. On the 25th day 30 cc. of whole blood was given. Blood serum at this time showed total protein 3.8 gm. per 100 cc., with albumin 0.5 gm. and globulin 3.3 gm., and serum cholesterol 525 mg. per 100 cc., with 242 mg. esterified. There was slight subsidence of the edema in the next 10 days, and the weight dropped from 1,595 to 1,400 gm. On the 29th day the hemoglobin was 14.5 gm. and the red blood cells 4,100,000. The E.S.R. was 25 mm. per hour (Wintrobe). Edema of the extremities and back disappeared but that of the face and neck persisted. The skin lesions resolved completely after incision, drainage and antibiotics. Penicillin and streptomycin were discontinued on the 33d day. From the 33d until the 45th day the patient received oxytetracycline (Terramycin), 100 mg. daily given orally. Vitamin and iron supplements were given. A whole blood transfusion of 30 cc. was given for anemia (hemoglobin 11.4 gm., RBC 2,410,000) on the 46th day of life. Funduscopic examination revealed no significant changes.

On the 71st day of life a transfusion of 40 cc. of whole blood was given because of anemia (hemoglobin 7.9 gm. per 100 cc., red blood cells 2,130,000) and hypoproteinemia. The blood was introduced through a scalp vein and shortly after completion of the transfusion, dyspnea and

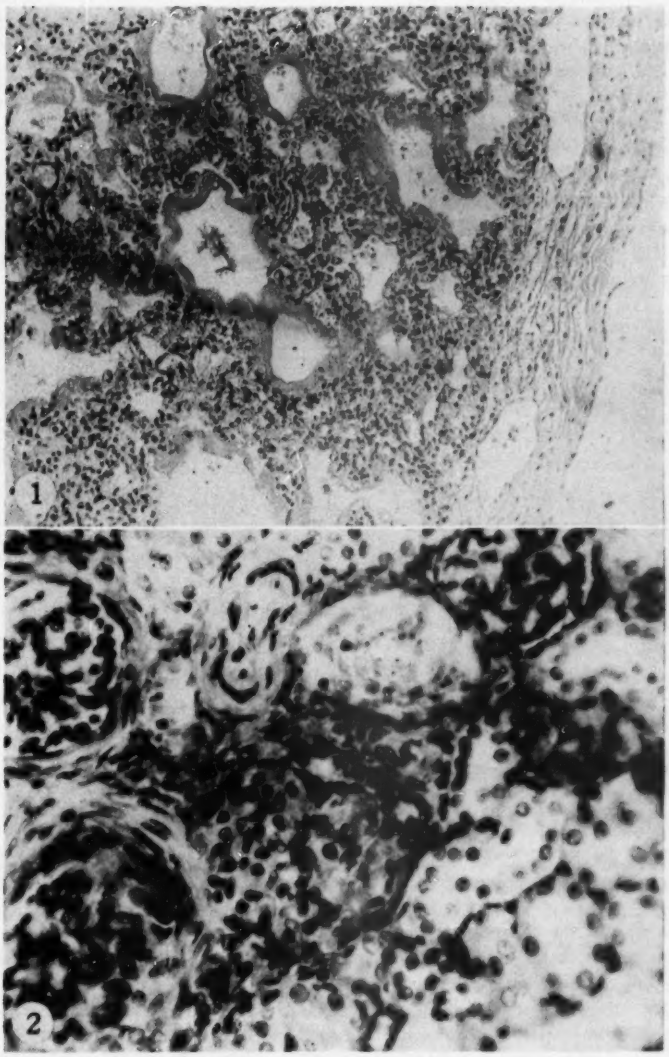

Fig. 1.—Photomicrograph of lungs. Hyaline membrane lining alveoli and areas of focal atelectasis and emphysema; × 140.

Fig. 2.—Photomicrograph of kidneys. Swelling of glomeruli, increased cellularity, and in some areas, slight to moderate proliferation of the lining cells of Bowman's capsule. In an occasional glomerulus, there is fusion; × 280.

cyanosis appeared. A reddish-tinged urine was passed (but not collected) and frothy, bloody mucus appeared in the mouth. Oxygen was administered immediately and penicillin given, but the infant died about twenty hours later.

A urine specimen obtained shortly before death revealed 4+ albumin and a 4+ benzidine and guaiac reaction with 4 to 8 red blood cells per high power field. There were many coarse granular and an occasional degenerated cellular cast. A few casts contained fatty droplets. A thorough study of the transfused blood revealed no error in typing and cross-matching.

Autopsy.—Autopsy was done by Dr. Otto Saphir, Director, Department of Pathology. The significant findings are confined to the kidneys and lungs.

Grossly the kidneys were normal in size. Their capsules stripped with ease, revealing surfaces which were hyperemic and showed fetal lobulations. The cut surfaces showed fair differentiation between cortex and medulla, with a fairly prominent reddish corticomedullary junction. The cortex showed ill-defined yellowish streaking perpendicular to the outer surface. The pelves were not dilated. The ureters and urinary bladder appeared normal.

Fig. 3.—Photomicrograph of kidneys. Sudan III stain, showing swollen, granular, and vacuolated lining cells of the tubules containing large amounts of fat; × 140.

Microscopically, the glomeruli were quite swollen and very hyperemic; they appeared much more cellular than usual; a few of the glomeruli showed slight to moderate proliferation of the lining cells of Bowman's capsule, and in an occasional glomerulus there was fusion (Fig. 1). The tubular lining cells were swollen, granular, and vacuolated; a few tubules were dilated. The intertubular capillaries were distended and engorged with blood. There were large amounts of fat in the glomeruli, smaller blood vessels and interstitial connective tissue, and tubular lining cells (Fig. 2).

Grossly the lungs were normal in size. Their pleural surfaces were smooth and glistening. The cut surfaces showed moderate hyperemia and edema. There was a faint suggestion of ill-defined granularity on the cut surfaces. The trachea and bronchi contained gray frothy fluid.

Microscopically the lungs showed focal atelectasis and focal emphysema, with some rupture of the alveolar walls. There was marked hyperemia, with distention and engorgement of smaller blood vessels and alveolar capillaries. Some alveoli contained debris, some were filled with extravasated erythrocytes, and others contained pigmented histiocytes. In some sections, the

alveoli were lined by a dense homogeneous eosinophilic membrane; (Fig. 3). On differential staining, this material proved positive for polysaccharides, protein, and nucleoprotein. The bronchi were moderately to markedly dilated.

The pathologic diagnosis was subacute glomerulonephritis and intra-alveolar hemorrhage of lungs with hyaline membrane formation.

COMMENT

Although gross edema was not observed until the ninth day, in all probability the onset of the edema occurred earlier. Physiologic edema occurs not infrequently in newly born premature infants during the first week of life and clears spontaneously in from two to three weeks. Therefore, it might be difficult to differentiate physiologic from pathologic edema without laboratory studies, viz., blood chemical determinations and urinalyses. Unfortunately, our first urinalysis was not done until the 16th day of life and blood chemistry studies until the 22d day. However, in view of the severity of the edema noticed on the 9th day, we believe that pathologic changes in the kidneys occurred prior to this time and possibly were present at birth.

Our impressions are supported by Mitchell's statements [1] that "some infants may be born with inflammatory and destructive lesions of the kidneys or acquire them shortly after birth. . . . It is difficult to separate from actual kidney disease the clinical manifestations, albuminuria and cylindruria. As a matter of fact, these two phenomena are normal in the first few days of life, and for the most part these should be considered seriously only in those cases in which autopsy has been performed!" Mitchell further states: "To strengthen the belief that congenital nephritis may occur are those reported cases in which death has taken place in the first few months of life and chronic kidney changes have been found for which no reason could be discovered during the life of the infant. The nature of the histologic observations in the kidneys of some of the infants and even in some of the older children indicate a process of greater duration than the life of the patient." Mitchell believes that intrauterine nephritis or nephrosis in early life may not be manifest until later childhood, as initial damage may not be severe enough to cause death at once, and the kidneys may carry on until further demands are made upon them during various childhood infections.

From the standpoint of etiology of the nephritis in our case, so far as we were able to determine, the mother had no infectious disease during pregnancy and congenital syphilis in the infant was excluded. In some of the cases, circulating bacterial toxins in the mother have been suggested,† and in one case neonatal sepsis or toxins from an intestinal infection was considered.[2] None of these conditions was present in our case. In the three cases of neonatal nephritis reported by Conrad, all of the patients had normal antepartum histories; all had convulsions and periodical cyanosis shortly after birth.[3] No blood chemical studies were done. The possibility of primary intracranial pathology—intracranial hemorrhage and/or anoxia—must be considered, particularly in view of the apparent recovery of two patients in a short period of time and the fact that there was no autopsy to confirm the diagnosis in the fatal case. The urinary condition alone may not have been significant (Mitchell).[1] Eiben and his associates [7] and Collins [8] came to no conclusions as to the etiology or pathogenesis of the nephritis in their cases.

† References 4 and 5.

The significance of the Staphylococcus skin abscesses in our case was considered. A renal pathologic process was evident long in advance of the skin infection. Whether or not this infection aggravated the existing nephritis is a matter of conjecture. Clinically, the infant showed no signs of deterioration at the time of, or after, this infection, and at autopsy no proof of this possibility was demonstrated.

Clinically, the infant revealed the classic nephrotic syndrome, viz., edema, hypercholesterolemia, hypoproteinemia, with low serum albumin and little change in the globulin, absence of significant azotemia, albuminuria, and cylindruria. The serum vitamin A level was elevated, as observed in the nephrotic syndrome by Kagan and Kaiser.[9] The persistence of red blood cells in the urine, although always few in number, indicated glomerular involvement. Blood pressure determinations were attempted on several occasions without success. Funduscopic examinations revealed no significant changes. The infant appeared to be improving clinically at the time of his accidental death after a blood transfusion administered because of anemia and hypoproteinemia. He was taking his feedings well and edema had subsided considerably. His cry was vigorous and he was not apathetic.

The cause of death provoked considerable speculation. A thorough study of the transfused blood and equipment revealed no error in typing or cross-matching and no evidence of contamination, bacterial or pyrogenic, so that death due to a transfusion reaction was eliminated. It was our impression that in all probability death was precipitated by acute cardiac dilatation and pulmonary edema due to the administration of a relatively large amount of blood (40 cc., approximately 13.3 cc. per pound body weight) too rapidly. Although the heart was not remarkably enlarged at autopsy, there was evidence of interstitial pneumonia, edema, and hemorrhage in the lungs. The presence of interstitial pneumonia and pulmonary hyaline membrane probably contributed to the pulmonary embarrassment and were significant factors in the death of the infant at the time of the transfusion.

SUMMARY AND CONCLUSIONS

The nephrotic syndrome in a 1,320-gm. newly born premature infant is reported. The literature relative to neonatal glomerulonephritis is reviewed and our case is the first in which the disease has been described in a newly born premature infant. Although gross edema was not observed until the ninth day, it is believed that the onset of the disease occurred earlier and possibly the disease was congenital in origin.

The infant died suddenly after a blood transfusion on the 72d day. There had been no "transfusion reaction," and it was felt that death was precipitated by an overloading of the circulation with too much blood given too rapidly—resulting in myocardial weakness and/or pulmonary edema, superimposed on interstitial pneumonia and hyaline membrane formation.

Autopsy revealed subacute glomerulonephritis with tubular degeneration. A large amount of fat was present in the glomeruli, smaller blood vessels, interstitial connective tissue and tubular lining cells. In addition to areas of focal atelectasis, emphysema and hemorrhage, the lungs showed marked eosinophilic hyaline membrane formation.

Miss Evelyn Lundeen, R. N., and her staff assisted in the procedures in the case reported, and Dr. Benjamin Kagan, Chairman of the Department of Pediatrics and Director of Pediatric Research, helped in the preparation of this paper.

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ACUTE EPIDURAL HEMATOMA IN INFANTS

Brief Review and Report of a Case

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EPIDURAL hematoma is well recognized as occurring most frequently in young and middle adult life and infrequently in childhood. The following case is reported to stress that such a lesion may follow craniocerebral trauma in a very young child.

REPORT OF A CASE

C. H. (Case E-27015) was seen soon after admission to the neurosurgical service of the Columbus Hospital on referral by Dr. J. A. March, of Shelby, Mont. The following is the initial history and neurologic findings and impression dictated at that time (about 3 a. m., July 5).

"This child was said to have been entirely well until about 9 p. m., July 4, 1953, when she fell from the cab of a pick-up truck, incurring a head injury. The truck was not moving at the time, and the injury was a result of the fall only. The child was said to have cried immediately and seemed to be all right when seen by a physician soon afterward. The parents were sent home with advice to watch the child closely for vomiting or other changes. According to the parents, the child seemed to be moving both sides equally at that time and was conscious and even crawled about to some extent. Within several hours, however, there seemed to be a definite deterioration in the state of consciousness, vomiting, and some increasing spasticity of the left side. The child was seen again by the family physician who immediately arranged transfer here.

"Neurologic examination: This is a well-developed and well-nourished girl 15 months of age, unconscious, but occasionally crying and responding to some extent on painful stimuli. There is extensor rigidity and spasticity of the left side, the upper extremity being extended in decerebrate posture rather than decorticate. Rather frequent aimless kicking movements, which appear restless in nature, are noted in the right lower extremity. There are also some occasional spontaneous movements of the right arm. The left pupil is distinctly larger than the right. The head is turned sharply to the left side, and passive motion to the right is resisted. Knee jerks are brisk bilaterally, and the Babinski sign is present bilaterally, also, possibly somewhat stronger on the left. Routine skull films disclosed no definite fracture. There is some contusion and ecchymosis in the left temporal region.

"Impression: Acute subdural hematoma, left. The anisocoria is probably a more reliable lateralizing sign and the left hemidecerebrate posture probably a result of contralateral shift to the brain stem. Some of the history obtained from the parents may not be entirely reliable, but some definite progression appears evident and exploratory trephines and probable subtemporal decompression certainly appear indicated at this time."

While the operating room was being prepared, skull films were obtained in anteroposterior, posteroanterior, Towne, and both lateral projections, disclosing no abnormality. These films were subsequently also reported as normal by the radiologist, Dr. F. M. Petkevich.

The possibility of an acute epidural hematoma was not strongly considered in the differential diagnosis largely by virtue of its infrequent occurrence in very young children and in this case also because of the normal roentgenological findings. Acute epidural hematoma of the classic type is practically always associated with a linear fracture of the temporal squama and occasionally with diastatic fractures of the squamosal suture. The rapid development of symptoms in this case however, was quite compatible with the usual sequence of events noted in acute epidural hematomas. Such a fulminating cerebral compression occurs in massive subdural hemor-

rhages and was alone not regarded as a point of significance in the differential diagnosis. In retrospect, it is felt that the sequence of events and neurologic findings in this case should be regarded as characteristic of an acute epidural hematoma, and such a diagnosis should be entertained particularly in those cases having evident fracture of the temporal squama or diastasis of the cranial suture lines.

Surgical exploration, initially through a trephine opening, of the left parietal area disclosed a typical epidural clot of rather firm "currant-jelly" consistency. The incision was extended down and a conventional subtemporal decompression was accomplished, exposing a very large epidural clot, in all particulars resembling that seen in adults and as large, probably amounting to at least 3 to 4 oz. (90 to 120 cc.). This massive collection of clotted blood extended well down into the middle fossa and far posteriorly over the surface of the tentorium. The hematoma was completely evacuated with suction and irrigation, and the source of the bleeding was identified as a laceration of the posterior portion of the middle meningeal artery by a diastatic separation of the left squamosal suture. There was massive displacement of the brain by the hematoma, exposing the left side of the cranial cavity from the frontal fossa and sphenoidal wing to the superior surface of the tentorium, the depth of the hematoma appearing to be at least 2 to 3 cm. from the surface of the skull in its deepest portion.

The postoperative course was quite benign except for a single convulsive seizure on the first postoperative day. Sutures and epidural drain were removed on the second postoperative day. The patient seemed to have made a practically complete recovery by the time of discharge from the hospital on the 12th postoperative day and was neurologically normal at that time.

When seen on follow-up examination three months later, the child was apparently completely asymptomatic, alert, active, and neurologically normal except for the mother's statement that occasionally when the child is tired there appears to be a slight tendency for the right eye to turn in. No defect in extraocular movements could be noted on examination. The child was discharged from further care by me and returned to the care of the family physician.

COMMENT

Epidural hematoma usually occurs in young and middle adult life. In children it is very infrequent, Munro and Maltby [1] reporting only 1 in the first decade in life in a series of 44 case of acute epidural hemorrhage at the Boston City Hospital. Gurdjian and Webster,[2] in their excellent review of the entire subject of extradural hemorrhage, mentioned that the occurrence of this lesion in the newborn is rare and that "extradural hemorrhage in infancy is also rare, and review of the literature reveals few instances of hemorrhage in the middle meningeal distribution." The rarity of epidural hemorrhage in children is further emphasized in the review of this problem by Campbell and Cohen,[3] who encountered anly 20 cases in a series of 1,136 consecutive admissions for head injuries to the Children's Medical Center in Boston, an incidence of 1.8%, compared with approximately 3% of all head injuries, regardless of age group, as reported by Munro and Maltby.[1] Ingraham [4] and co-workers emphasized that occurrence of epidural hemorrhage is less frequently recognized, "the literature being confined to isolated case reports." They quote Munro and Maltby, Peet, and Gurdjian that "the lesion is a rarity in the pediatric age group." They report 20 patients younger than 12 years of age among approximately 1,000 patients with head trauma.

In reviewing the series of Campbell and Cohen,[3] only 9 of the 20 cases reported occurred during the first two years of life, if 1 case of birth trauma is excluded, and only 2 additional cases occurred under the age of 6 years.

Goode [5] reported a typical case of middle meningeal hemorrhage in a child of 13 months and states that he could find only 1 previously recorded case in a child so young, the latter case reported by Wakely and Lyle in their report on 14 instances of extradural hemorrhage.

In spite of the obvious infrequency of typical epidural hemorrhage in children as a sequal to craniocerebral trauma, it should be recognized that such an urgent surgical emergency may be encountered in very young children and, further, that such lesions may be occasionally observed with a typical history and neurologic findings characteristic of acute epidural hematoma as encountered in adults.

SUMMARY

A case of acute epidural hemorrhage is reported in a 14-month-old child occurring secondary to trauma with a typical "free interval" and the subsequent development of symptoms and signs which in all particulars, including the surgical pathology, resembled typical epidural hematoma in an adult. It is emphasized that the relative infrequency of such lesions in infants might lead to unjustified complacency in this regard in cases of craniocerebral trauma in infants. The same careful observation and precautions as taken in adults is strongly advised. A brief review of the literature on the infrequent occurrence of acute epidural hematoma in infants is given.

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Society Transactions

SOCIETY FOR PEDIATRIC RESEARCH

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Observations on a Disturbance of Tryptophan Metabolism Associated with Congenital Hypoplastic Anemia. DR. KURT I. ALTMAN (by invitation) and DR. GERALD MILLER. Rochester, N. Y.

Studies of a patient with congenital hypoplastic anemia have demonstrated a disturbance of tryptophan metabolism resulting in the excretion of anthranilic acid in the urine. Oral administration of *l*-tryptophan in this patient led to increased excretion of anthranilic acid. This substance has been detected in urine specimens made available to us from eight additional cases under observation by other investigators. Urinary excretion of anthranilic acid resulting from disturbed tryptophan metabolism appears to be a feature common to children with this disorder and has not been observed in normal children or in children with other varieties of chronic anemia. These and other observations suggest an association between congenital hypoplastic anemia and an inborn error of tryptophan metabolism. The findings offer a new approach to the investigation of the hematologic disorder, as well as an opportunity to study a variety of pathologic metabolism of tryptophan in the human.

Thus far therapeutic efforts directed at modifying the metabolism of anthranilic acid have not affected the anemia, although the excretion of anthranilic acid has been altered. Data obtained during these therapeutic trials will be presented. Certain hypotheses relating the failure of erythropoiesis to the metabolic abnormality will be discussed.

DISCUSSION

DR. HUGH WILSON JOSEPHS, Baltimore: In Baltimore last year, we had a child who came in at the age of 5 months with what was at the time thought to be a congenital hypoplastic anemia of this type, and the bone marrow showed no reduction in the red cells.

He had been carried along with transfusions up to that time, and he was given transfusions in the hospital; after the diagnostic studies, he was sent home. He came back a month later, at the age of 6 months, again for transfusion. This time, however, his hemoglobin did not fall, and he was sent home again. As far as I know, he is now developing perfectly well, that is, the last I heard of him, three or four months ago, he was developing all right, and this thing had not returned.

That brought up the question of whether he had simply a failure of red cell formation, which results during the first two or three months from the necessity to reduce the hemoglobin and red cells from the high level at birth; there is a physiological mechanism in the body by which red cells are reduced from their high level, which at the age of 2 or 3 months is normally recovered from. This child had simply gone on for several months more with the hypoplastic phase.

The thing that interested me was that there was no way, at the time he came in, of distinguishing congenital hypoplastic anemia from this hypoplastic phase of the physiological anemia. I wonder if it wouldn't be worth while to carry these studies out in the phase of physiological hypoplastic anemia that occurs in the first month or two of life. I wonder if that has been done, or whether it was intended to be done.

DR. CARL H. SMITH, New York: These observations are of primary importance, since they provide a new approach in the investigation of a baffling group of anemias. Reported cases and information obtained from a recently circulated questionnaire confirmed our impression that

hypoplastic anemia can no longer be regarded as a single entity but comprises several conditions. We have termed as "pure red cell anemia" cases dating from birth in which the failure of hematopoiesis is restricted entirely to erythropoiesis, without simultaneous impairment of leucocytes or platelets. In this type only an occasional nucleated red cell appears in the bone marrow. In the cases reported as "erythrogenesis imperfecta," red cell production is depressed, but not to the same extent as in the former, since the bone marrow reveals moderate numbers of nucleated red cells. Cases also described as hypoplastic anemia show a normal bone marrow with varying grades of peripheral anemia, while others are associated with a decrease of normoblasts in the bone marrow, a lesser reduction of other bone marrow components, and a poor prognosis.

The data presented by Dr. Miller indicating a disturbance of tryptophan metabolism suggest the possibility that this finding may serve to differentiate the various entities, perhaps separating the cases that respond to cortisone or splenectomy or both. One of our own cases included in Dr. Miller's series was that of "pure red cell anemia" which did not respond to either measure.

DR. ROBERT A. ALDRICH, Portland, Ore.: The results of administering diathermy to a patient of this type were presented by Dr. Edward Nelson and me to this Society a few years ago. This child is now completely well, but it is of some interest that a younger sibling was born with the same disease, and she, too, has responded to this form of therapy and is able to get along now without any treatment at all. In view of the fact that little is known about the cause of this disease, it may be of interest to observe the effect of diathermy on the metabolic disturbance which has just been described.

DR. RALPH V. PLATOU, New Orleans: I should like to ask the authors if any of the 15 patients were of the classic "Fanconi variety." I ask this because we have, I think, an experimental model in sisters. The older has the classic and severe aplastic anemia with congenital deformities. The younger has identical deformities, but no anemia. It occurred to me that this metabolic error might be of prognostic import in relation to the problem in the younger child.

DR. JOSEPH DANCIS, New York: I wonder if Dr. Miller had the opportunity to determine whether the tryptophan levels in the blood of these patients were higher than normal.

DR. CHARLES D. MAY, Iowa City: I should like to ask if the authors had an opportunity to try the effects of withdrawal of tryptophan or other precursors from the diet, on the assumption that whenever one of these amino acids is not properly metabolized, toxic effects may be revealed and eliminated by withdrawal.

DR. GERALD MILLER, Rochester, N. Y.: In answer to Dr. Josephs' question, we had in mind to examine with tryptophan loading both the infants during the second and third months, during the occurrence of the so-called physiologic anemia accompanied by some degree of hypoplasia, and particularly the marked degree of that process seen in premature infants. We have no data in either of those groups.

Dr. Smith, one of the cases of Dr. Cathie, in London, from whom he sent us some urine, was one he described with numerous nucleated red cell precursors in the bone marrow. I don't recall at the moment whether this child had constantly any normoblastemia of the peripheral blood.

The two cases we examined personally almost have no nucleated red cells in the marrow.

I remember Dr. Aldrich's report. Our little girl was treated with diathermy, and the only net effect was that unfortunately she urinated while she was being treated and has a severe burn on her body. I think that would not discourage me personally from trying the same treatment, but I would surely be careful with it.

Dr. Platou, the one case of Fanconi's pancytopenia with multiple congenital defects I included in the group of miscellaneous aplastic anemias. That girl did not show any of the abnormal metabolites of tryptophan in her urine.

I was very much interested, indeed, in your two cases, and I think another biologic model exists in a strain of mice that has been fascinating us recently in which, by appropriate genetic maneuvers, one can achieve a number of different effects, including anemia, and disturbance of gonadal development, and so on, and disturbance of coat color.

Dr. Dancis, I am sorry, but the answer is no.

I must answer Dr. May's question with "no." We have not tried the withdrawal of tryptophan from the child's diet. We have not modified the diet in any way. I think that is a very interesting suggestion. I am grateful for it.

Vitamin B_6 Requirement in Relation to Convulsive Seizures in Infants. Dr. Doris J. D. Adams (by invitation), Dr. O. A. Bessey (by invitation), Dr. D. R. Bussey (by invitation), and Dr. A. E. Hansen, Galveston, Texas.

The observation has been made that certain infants developed convulsions when maintained on a milk preparation designed to simulate breast milk in composition. Pyridoxine was found to be effective in alleviating the spasms. The question arises as to whether this phenomenon occurs because of a low convulsive threshold or reflects a high requirement for vitamin B_6. Deficiency of vitamin B_6 results in the incomplete metabolism of protein, and one method of measuring the status of this vitamin in the body is to determine the urinary excretion of xanthurenic acid following the administration of *dl*- or *l*-tryptophan. In order to ascertain the possible significance of individual variation in vitamin B_6 requirement as playing a role in the occurrence of convulsions, the following studies were undertaken. *l*-Tryptophan was administered to 11 infants, and some 50 determinations of xanthurenic acid excretion in the urine were made. Particular attention was paid to the findings in three infants, two of whom suffered convulsions while receiving the convulsigenic milk mixture. Case 1, a 7-month-old infant, had daily convulsive seizures, beginning at 4 months of age. No change had been made in the milk mixture or type of feeding, but anticonvulsant drugs had been of no benefit. This infant was kept on the milk preparation which was from the same lot known to have been fed to some infants who had had convulsions. Repeated analyses for xanthurenic acid excretion were positive until the intake of pyridoxine reached 1.2 mg. Case 2, a 4-month-old white boy, had suffered 12 convulsions since the age of 1 month. While in the hospital, six seizures were noted within a four-day period. Pyridoxine was given, 10 mg. daily orally, with prompt cessation of symptoms. Twelve days after the pyridoxine had been discontinued, it was found that xanthurenic acid was excreted following a test dose of *l*-tryptophan. Case 3, a 3-month-old healthy infant, was used as a control and maintained on the same milk mixture. Xanthurenic acid excretion was tested periodically. No convulsions occurred during the two-and-one-half month period he received the milk. However, within three weeks xanthurenic acid appeared in the urine when *dl*-tryptophan was given. Supplements of pyridoxine indicated that this infant needed only about one-fourth the amount of pyridoxine which had been required by the first infant to suppress the excretion of xanthurenic acid. Pyridoxal and pyridoxamine in equivalent doses to pyridoxine had the same effect both in Case 1 and the control subject, Case 3. Single determinations were made on an additional eight control infants who were receiving an evaporated-milk mixture. None of these had had convulsions, and in each instance, save one, no xanthurenic acid was excreted. Our observations suggest that (1) vitamin B_6 requirement is distinctly higher for some infants than for others; (2) when a milk preparation supplies less than 0.2 mg. of vitamin B_6 per day, it may lead to abnormal symptoms; (3) the amount of vitamin B_6 supplied in an evaporated-milk mixture does not seem to offer a wide margin of safety for some infants.

DISCUSSION

Dr. David B. Coursin, Lancaster, Pa.: I should like to congratulate Dr. Adams and Dr. Hansen on their biochemical work in this problem. I think they have contributed a great deal toward gaining some answer to the changes in the underlying biochemistry and electrophysiology.

We have been impressed with the rapidity of these changes and have also been concerned with the effects of vitamin B_6 administration in these patients. Our series has now been followed from 4 to 30 months and has provided some information on certain aspects of long-term follow-up in this problem.

It appears from clinical evaluation and electroencephalographic studies that these youngsters have shown normal patterns of growth and development since correction of their seizures. There have been no residuals of central nervous system damage or convulsive seizures in patients who were adjudged normal originally. Furthermore, none of the symptoms that Dr. Adams listed as appearing in vitamin B_6 deficiency, such as anemia, changes in growth, and weight loss, were manifest in any of our patients.

A second point of interest deals with the prolonged effect of large doses of vitamin B_6 in preventing an exacerbation of these seizures. This observation was made in a patient who exhibited status epilepticus with improvement within 60 seconds following intramuscular injection of 100 mg. of pyridoxine. The patient was maintained on the original vitamin-B_6-deficient diet

for 84 days following this injection, with no recurrence of seizures during this time. This was in contrast to the child's previous relapses within 48 hours when doses of 100 to 200 γ of B_6 were given orally.

DR. ANDREW D. HUNT JR., Flemington, N. J.: The problem of varying requirements for vitamin B_6 in infancy, brought up by Dr. Adams, is a most interesting and important one.

Stokes, McCrory, Stroud, and I recently reported a case of an infant who developed serious convulsions shortly after birth. It was subsequently demonstrated that the convulsions were relieved by a daily maintenance dose of 2 mg. of pyridoxine. Thus, this was an infant demonstrating an abnormal need for pyridoxine in the neonatal period. Of great interest to us was the fact that the mother of this infant had been given large doses of pyridoxine during the first four months of pregnancy for the relief of nausea and vomiting. In an attempt to test the possibility of a relationship between this history of pyridoxine medication during pregnancy and the pyridoxine requirements of the infant, we have been working with pregnant rats, loading them during the first three-fourths of their pregnancy with 10 mg. of pyridoxine hydrochloride daily, and thus far have observed no effect on the incidence of convulsions in the suckling newborn animals with the mothers, after giving birth, on a pyridoxine-deficient diet. These studies are not yet completed.

Regarding the paper of Dr. Adams and her associates, one might possibly question the reliability of the xanthurenic acid test as an absolute measure of pyridoxine requirement. Wachstein has demonstrated positive xanthurenic acid tests during normal pregnancies in women on presumably adequate diets. Although the findings are reversed by the administration of pyridoxine, it is open to question whether such a biochemical finding can be interpreted as an indication of a vitamin deficiency in pregnancy.

Rosen has shown that convulsions can be produced in rats by the administration of isoniazid. Such convulsions are relieved by the administration of pyridoxine. However, xanthurenic acid tests are negative in these convulsing animals. The infant described by us, likewise, although suffering from convulsions relieved by pyridoxine, gave a negative xanthurenic acid test.

The interpretation of Dr. Adam's data, it seems to me, is further complicated by the appearance of a positive xanthurenic acid test in one of her normal control infants.

In any case, in view of the inconstant nature of the relationship between the positive xanthurenic acid test and symptoms relieved by pyridoxine, it seems to me that great caution should be exercised in the interpretation of data based on this test.

DR. CHARLES D. MAY, Iowa City: Having felt it proper to be critical earlier in the week of one phase of this work, I am happy to rise and express appreciation of this phase. This is very much needed data, and one of the few bits of data which was gathered during this very dramatic episode of convulsions which occurred throughout the country.

This is a vitamin which can be synthesized by bacteria that ordinarily inhabit the gastrointestinal tract. The dietary intake does seem to have some critical level, in contrast to folic acid, where the dietary requirement can be very minimal.

We do need more information concerning what the excretion of vitamin B_6, which might have been synthesized, is in such an instance and the relationship between the composition of the diet and synthesis by the organisms. One bit of quantitative data in this respect of which I am aware indicates that in general infants excrete more pyridoxine compounds than they take in. Nevertheless, it is still of interest that in the case of B_6 these minor changes in levels in the diet do seem to have profound implications.

DR. GERALD MILLER, Rochester, N. Y.: I just wanted to ask the speaker whether the urines of any of these infants were examined other than for xanthurenic acid.

DR. SAMUEL P. BESSMAN, Washington, D. C.: The only reaction characteristic of brain with which pyridoxine is connected, and this is a very close connection, is the decarboxylation of glutamic acid to γ-aminobutyric acid. This reaction is found in no other tissue, and it is specific for pyridoxine, or pyridoxal, which acts as a coenzyme for the decarboxylation.

Further reactions of γ-aminobutyric acid involve a specific transamination with ketoglutaric acid to form a very peculiar intermediate, succinic semialdehyde, quite active also in brain metabolism.

I should be very interested to know whether or not the xanthurenic acid excretion merely reflects one of the many functions of pyridoxine that we know of, such as serine dehydration,

tryptophan metabolism, and the transamination reaction with glutamic acid. Xanthurenic acid excretion might be merely an indication of pyridoxine deficiency, rather than an indication of the lesion relating to the convulsion. This is of importance because as far as I know xanthurenic acid has not been demonstrated to be an intermediate in brain metabolism, whereas both glutamic acid and γ-aminobutyric acid transamination, both dependent upon pyridoxine, have been shown to be specific for brain.

Dr. Doris J. D. Adams, Galveston, Texas: In relation to Dr. Coursin's question, an electroencephalogram indicated an abnormal pattern in only one patient, and these findings disappeared after the administration of pyridoxine. This occurred in the infant whose mineral balance studies were reported by Dr. Hansen on Monday. In our experience, giving the infants a milk containing 0.6 mg. of vitamin B_6 caused cessation of seizures, but excretion of xanthurenic acid continued until higher levels of pyridoxine were given. Weight gain was slow in our patients, and only one patient developed an anemia, despite supplemental iron. We felt that the intake of vitamin C had been too low, and the bone marrow, in part, confirmed this, as the findings were those of a megaloblastic anemia.

Yes, Dr. Hunt, we also had one child whose mother had had vitamin B_6 during her pregnancy, but for the most part the mothers of our infants had no serious nausea and vomiting and had received no added vitamins orally or parenterally. Most of our children were from very low income groups. The infant delivered by Caesarean section because of eclampsia was not a breast-fed infant. This child was hospitalized because of prematurity, and he was used as a control subject. It was the second of the convulsing infants who was breast-fed and responded to the administration of vitamin B_6.

In reference to Dr. May's question, we have only studied the excretion of xanthurenic acid. Studies on pyridoxic acid content of the urine and work with experimental animals are now in progress. The idea behind the presentation of xanthurenic acid excretion data was not because we felt that tryptophan metabolism per se resulted in convulsions. Vitamin B_6 is a widely utilized enzyme, e. g., in decarboxylation, sulfdehydration, and transamination. However, it is apparent that the ability to handle tryptophan is one method of measuring the adequacy of vitamin B_6 intake.

Agammaglobulinemia: An Experimental Study. Dr. Robert A. Good, Minneapolis.

Bruton's discovery of a disease syndrome characterized by recurrent severe bacterial infections associated with absence of circulating gamma globulin and failure of antibody production has provoked fruitful search in many centers for patients suffering from agammaglobulinemia. Two such patients have been studied in our laboratory. Both were subject to recurrent infection; neither possessed demonstrable gamma globulin; no evidence of tissue or serum antibody could be found, and both lacked isoagglutinins against heterologous blood groups. Intense antigenic stimulation with a variety of antigens was not productive of circulating antibody.

Although deficiency of tissue lymphocytes and absence of germinal centers in lymph nodes have been proposed as a basis for the disorder, the pathogenesis of agammaglobulinemia has not been established. Current evidence suggests but does not establish the congenital nature of the disease.

Much evidence linking plasma cell formation with production and release of gamma globulin and antibody has been accumulated in recent years. To gain further evidence on this point, response of the bone marrow and regional lymph nodes to intense antigenic stimulation was compared in patients with agammaglobulinemia and in normal children and adults. Plasma cells, found in small numbers in bothe the lymph nodes and bone marrow of normal subjects, increased significantly following antigenic stimulation. No plasma cells were found in initial biopsies in the patients with agammaglobulinemia, and plasmacytosis did not occur after intensive antigenic stimulation with typhoid-paratyphoid antigens. Control subjects showed significant rise in titer to the antigens, whereas no antibody or gamma globulin appeared in the patients with agammaglobulinemia.

Several workers have proposed that C-reactive protein represents "natural antibody," and it has been suggested that this protein is involved in antibody production. The patients with agammaglobulinemia formed C-reactive protein in the same quantities as were produced by control subjects in response to comparable stimulation.

Prior investigations have suggested that refractoriness to the pyrogenic action of Gram-negative bacterial endotoxins does not involve antibody production. Proof of this dissociation has been lacking. Both of the patients with agammaglobulinemia developed refractoriness to systemic intoxication, leucocytosis, and febrile effects of typhoid-paratyphoid endotoxins with the same facility as did control subjects.

Finally, the basis for rejection of homologous tissues and organs has not been established. It has been postulated that failure of homologous grafts to take has an immunological bases. A 100% take of both full-thickness and split-thickness homologous skin graft has been accomplished in a child with agammaglobulinemia. This graft has remained in place for eight weeks, whereas the patient's skin grafted onto a normal child suffering from burns took at first and then sloughed completely between three and four weeks after being applied.

These data are interpreted to indicate that (1) plasma cells are directly associated with ability to form antibody; (2) C-reactive protein is probably not associated with a function of plasma cells or with the formation of antibody; (3) refractoriness to Gram-negative bacterial endotoxin does not involve circulating antibody; (4) it is probably possible to homograft skin in patients with immunoparalysis.

The Response of Lymph Nodes of Normal and Congenitally Agammaglobulinemic Children to Antigenic Stimulation. Dr. John M. Craig (by invitation), Dr. David Gitlin, and Dr. Theodore C. Jewett (by invitation), Boston.

Since the first case of agammaglobulinemia was described by Bruton, in May, 1952, with the characteristic history of recurrent bacterial infections, evidence of deficient antibody formation, and very low serum levels of gamma globulin, more than 16 cases have been discovered. Because these children have a normal rate of degradation of administered gamma globulin, an investigation into the cellular responses to injected antigens was carried out.

Lymph nodes were removed at herniorrhaphy from otherwise normal children who had received subcutaneous injections of combined diphtheria, pertussis, and tetanus antigen (0.5 cc.) and typhoid-paratyphoid vaccine (0.5 cc.) four days before operation. These lymph nodes histologically showed an increase in the breadth and cellularity of the nodal cortex and the development of well-defined follicles having active germinal centers. The medullary cords were increased in prominence, and large numbers of plasma and preplasma cells appeared in both the cortex and medullary regions. Sections of these lymph nodes examined by the fluorescent antibody technique revealed gamma globulin in various cells and in the interstitial fluid; pertussis antigen could easily be demonstrated in the reticuloendothelial cells. Specific antibodies versus diphtheria and tetanus toxins were to be found in cells of the plasma cell series.

Lymph nodes removed from similarly treated children with congenital agammaglobulinemia showed, in comparison, a much narrower cortex, small ill-defined follicles, an absence of germinal centers and of preplasma cells, and plasma cell forms. The reticuloendothelial cells of the peripheral and central sinusoids in these nodes were swollen. When examined by the fluorescent antibody technique, administered antigenic material was easily demonstrated in these nodes, but neither gamma globulin nor specific antibody could be found.

A similar depletion of the lymphoid tissue and an absence of members of the plasma cell series has been observed in postmortem material in two cases of agammaglobulinemia.

These findings indicate that in congenital agammaglobulinemia there is a deficiency in the production of the cell forms responsible for the formation of antibody.

DISCUSSION

Dr. Bela Schick, New York: I want only to talk about the possibility that besides these beautiful cases of complete absence of gamma globulin, there are other forms which occur. First, you have fluctuating of gamma globulin, within the serum, and then you have to think about the factors that gamma globulin may be present, but the gamma globulin doesn't contain the specific antibody, so that immunity may be depending upon the absence or presence of specific antibodies.

Dr. Janeway will tell you about the higher level of gamma globulin. I should like to mention that the first case of congenital absence of gamma globulin published was of a child 2 years old.

The fact was that this child showed an anomaly of the liver which consisted of absence of part of the liver tissue, with no inflammatory necrosis, just the congenital form of the malformation of some absence of liver tissue.

I have described one case, at that time 20 years of age, that I had followed up since birth. The child had congenital edema, and, curiously enough, this child had no susceptibility to infection. To the contrary, this child was healthy and never missed a day in school. We would always joke that the name of the child was Ice, and I had to wait 20 years until I broke the ice of the father for hospitalization of the child. There we found that the child has no gamma globulin, only intensive edema. This child was incapable of reproducing antibodies. There is no doubt that there are congenital forms showing the synthesis of gamma globulin to be deficient. There have been cases cited recently of gamma globulin deficiency that have a high rate of immunity. This immunity may be due in these cases not to the presence of antibodies in the serum, but to other forms of immunity.

Dr. Charles A. Janeway, Boston: I should like to congratulate Dr. Good, because he has done the sort of study which we hoped would be done when we described a number of these patients. This disease provides an experiment of nature which is analogous to these errors of metabolism discussed in the presidential address. In pediatrics we have unique opportunities to study certain fundamental biological processes as a result of observing patients in whom there are such specific metabolic defects.

It is gratifying to note the close similarity in the observations that have been made by both groups of workers in regard to the pathologic responses to immunization.

A patient quite similar to the ones Dr. Craig has presented was described by Dr. Donahue, at Toronto, not under the name of agammaglobulinemia, but under the term alymphocytosis, a couple of years ago. Until we have a chance to study the blood of Dr. Schick's patient by suitable sensitive techniques (immunochemical rather than electrophoretic), I should'nt accept the fact that his patient has true agammaglobulinemia.

When we study these patients, they seem to fall into two groups. There is first what we call a congenital group. These patients are all males. Whatever evidence we have about heredity indicates that this is similar to that of hemophilia, namely, that the condition passes from generation to generation by way of an unaffected mother; evidence for this is not conclusive, but is piling up all the time.

The field is confused by the fact that it is clear that one can also have acquired agammaglobulinemia from various causes, most of them at present unknown. The oldest patient we know about with this syndrome is 79 years of age, but we have observed several cases in children which we feel are of the acquired type, and one of Dr. Good's two patients has an acquired case. In this group both sexes are represented.

In agreement with Dr. Schick, I should say that I am sure there is a whole spectrum here, and we are just beginning to scratch the surface.

Dr. Vincent Kelley, Salt Lake City: I should like to ask Dr. Craig on what basis he can say that the agammaglobulinemia in these patients is congenital. If this is based only on its early appearance, I doubt that congenital agammaglobulinemia occurs only in males, since we have a female patient whose symptomatology of agammaglobulinemia appeared at the age of 3 months.

Dr. Joseph Stokes Jr., Philadelphia: I should simply like to add how splendid I feel these papers are. Dr. Good's developments are particularly interesting.

One point I think is worth mentioning. I don't want to enter into the plasma cell controversy, but I think it is of considerable interest to mention the fact which I touched on yesterday, that apparently if one grows lymphoid tissue, the lymphocytes disappear and reticular cells proliferate and develop into lymphocytes.

The Drs. Harris have done very interesting work in transfusing to irradiated rabbits suspensions of lymph node cells which were very largely lymphocytes and have shown very high antibody titers after four days.

If Dr. Good is correct concerning the plasma cell, either the lymphocytes then change into plasma cells, and form antibodies after that time, or there may be 1, or less, out of 1,000 lymphocytes that may be producing all of the antibodies.

The fact that the original cell is formed from the reticulum cell and may pass through the plasmacyte series and then to the lymphocyte, it would seem to me indicates that probably both cells are producing antibody when they are transfused in this way.

I should be interested in hearing Dr. Good's comments upon this fact. I think Dr. Craig's statement that the lymphoid cell as such, whether it is plasma cell or lymphocyte, is producing antibodies is a much safer consideration.

DR. HORACE L. HODES, New York: I wonder whether Dr. Good is contemplating implanting a lymph node in the patient he described. If it is true that the lymph node would "take," then some of the points Dr. Stokes raised might be answered.

For example, it would be interesting to see whether the patient would continue then to show plasma cells in his response to local injection of antigen, and it might help to settle this particular point.

DR. ROBERT A. GOOD, Minneapolis: Many interesting points have been raised in the discussion, a few of which I shall attempt to answer. With respect to Dr. Schick's comments, I can say only that in these patients other liver functions are normal, and biopsies of the liver reveal no abnormalities save a mild infiltration of pure lymphocytes in the portal spaces. I think it quite important to distinguish the patients being studied by Dr. Janeway and myself from the cases reported by Dr. Schick and Dr. McQuarrie a few years ago. Our patients have perfectly normal serum proteins, with the exception that they lack gamma globulin and cannot produce antibody.

The spleens in our patients show evidence of hyperplasia of the reticulum similar to that described in Craig's cases at autopsy. The lymphocytes seem to be deficient in the spleen, but they are present and appear to be developing in this organ.

In the bone marrow the number of lymphocytes present is similar to that characteristic of normal persons. In one of our patients, lymphocytes totaled 15% of the nucleated marrow cells, in the other, 17%. Although this evidence, together with that presented earlier, does not completely eliminate a generalized lymphoid deficiency as a basis for the immunological paralysis, it does indicate that in these patients the only series of cells lacking significant representation is the plasma cell group.

Putting this observation together with other evidence available in the literature permits us to venture the conclusion that the histological and hematological findings in the patients with agammaglobulinemia may be interpreted as evidence supporting the plasma cell theory of antibody formation.

Dr. Janeway mentioned that one of the patients studied is suffering from acquired agammaglobulinemia. We believe this to be the case. The patient is a 26-year-old girl who had no unusual trouble with infections until she was 18 years old. Since that time she has had 33 to 34 attacks of pneumonia, proved many times to be due to pneumococci. She had septicemia on several occasions, three attacks of bacterial meningitis, and numerous other severe bacterial infections.

This particular patient does not seem to be distinguishable in her immunological disturbance from the patient with congenital disease. Our other patient appears to have the congenital disease, since he has been in serious trouble from infection since he was 6 months of age.

With respect to the comments made by Dr. Stokes, we are indeed aware of Dr. Harris' work. It is, in fact, impressive to me how much antibody the recipient animals produce in response to the administration of a relatively small number of cells. There are a number of problems, however, that make it difficult for me to accept Dr. Stokes' interpretation of the results. One question which comes to mind is, are the cells being studied really lymphocytes? We have never been able to separate out lymphocytes in pure form from any source. We doubt if the Harrises have. As a matter of fact, we have never been able to prepare cell suspensions from lymph nodes which did not contain all the types of cells that have been implicated at one time or another in antibody production, i. e., hematopoietic reticulum cells, reticuloendothelial cells, plasma cell precursors, plasma cells, and lymphocytes. Consequently, if these are not pure cultures of cells, one has only to assume that plasma cells or reticulum cells are 30 to 60 times more active in antibody production than lymphocytes to interpret the findings thus far reported as evidence that either of the former cell types is responsible for antibody production.

Further, the system being studied is complicated. Transfusing cells, particularly complexes of cell types, and demonstrating consequent antibody production is far more indirect than the experiments done by Coons and Ehrich, which demonstrate directly that plasma cells contain and are liberating antibody.

Dr. Hodes's question is provocative. Yes, the justification for grafting the homologous skin was not only that it would provide information on the basis for transplantation failure in man but that the possibility of transplantation of lymphoid tissues in an attempt to cure the disease seemed worthy of trial if transplantation of skin was successful. Lymph node transplantation represents the next phase of our investigation.

DR. JOHN M. CRAIG: I think Dr. Good has already answered most of the questions. There are one or two things I might add. There appears to be a relative inactivity after antigenic stimulation in these lymph nodes. They do develop an increased number of lymphoid elements, but with a failure to produce plasma cells. This latter is a quite remarkable feature of the agammaglobulinemic patients. I think the lack of mitoses in the simulated lymph nodes from patients with agammaglobulinemia is also a very remarkable feature. I think that both elements, a failure to produce plasma cells and a total hyporeactivity of the lymphoid tissue, are important in the syndrome of agammaglobulinemia.

The Renal Lesion in Acute Metabolic Alkalosis. DR. MALCOLM A. HOLLIDAY, Fort Bragg, N. C., and DR. DALE SCHULZ (by invitation), Indianapolis.

Reduced renal function and histological lesions have been reported in patients with metabolic alkalosis. Histological lesions in renal tubular epithelium have been described in potassium deficiency in rats.

The present report is a description of similar lesions observed in acute metabolic alkalosis produced in rats by the intraperitoneal exchange of bicarbonate for chloride. For three days following this procedure, the animals were maintained on an electrolyte-free intake; during this period, cell potassium deficiency developed. Serum and muscle for analysis and viscera for histological examination were obtained at the end of the three days. On microscopic examination of the kidney, the distal tubular cells were observed to be quite swollen and to contain pale cytoplasm and large vesicular nuclei. Mitotic figures were present. These changes indicated an active proliferation.

Since the lesions developed after 3 days, additional groups after 12, 24, and 48 hours of alkalosis were studied. In the first 24 hours, degeneration and necrosis predominated. After that, the regenerative changes became evident.

Other groups, made alkalotic, were given various electrolyte solutions in place of drinking water to observe the effect on the degree of alkalosis, cell potassium deficiency, and renal changes. Sodium acid phosphate increased the alkalosis and potassium deficiency and greatly intensified the renal lesions. There was more pronounced swelling and mitosis, and in addition, there was calcification of the tubular cells. Sodium bicarbonate, while increasing the alkalosis and potassium deficiency, had no consistent effect on the tubular changes. Adding potassium bicarbonate to sodium bicarbonate did not alter the effect of the sodium bicarbonate, but potassium bicarbonate given alone did diminish all the observed changes.

The early appearance of changes suggests that the alkalosis per se is an initial factor leading to the changes. However, the effect of the various electrolyte solutions, especially phosphate, make evident the importance of additional factors or perhaps a sequence of changes in the full development of the lesion.

DISCUSSION

DR. WILLIAM M. WALLACE, Cleveland: I think that this paper is of considerable interest. It brings a chemical state into close correlation with a histologic lesion.

I had hoped that Dr. Holliday could give us some help in the controversy as to just what is the site of acidification of the urine. I had hoped that he would show us clear-cut lesions in either the proximal or distal tubules. I wonder if he has any ideas as to how a more definite pathologic localization can be obtained?

Another point worth noting is that the lesions are not diffuse, as one might expect, but sharply localized. A generalized metabolic state seems to have damaged some tubules and left closely contiguous ones undamaged. This has certain implications with regard to the interpreta-

tion, in terms of renal function, of the significance of urine that has been mixed in the collecting apparatus. How much does bladder urine tell us in terms of what the individual nephron is doing?

The Berliner group have recently given us a neat explanation of the high CO_2 tensions found in the urine of alkalotic subjects in just such terms. They point out that such high tensions can only be accounted for by the mixing of urines from nephrons lying side by side but functioning differenty. This has required some modification in our concepts of the mechanism of acidification.

Why does acid phosphate make the animals more alkalotic? Will Dr. Holliday speak about that?

DR. ROBERT COOKE, New Haven, Conn.: I think that these studies show some very important findings, some of which are new, I am sure. However, it has been known for a considerable period of time that rather extensive lesions can occur in the tubules with alkalosis. For that reason, three years ago, we studied all our cases of pyloric stenosis that we could bring back into the hospital to find out whether or not they had any functional lesion.

Exhaustive kidney function tests were not done, but they had no evidence of inability to regulate their acid-base balance, difficulties in concentrating urine, or evidence of any calcification in the kidneys.

I think the important contribution that Dr. Holliday has made is that he has shown here the effects of an increased amount of sodium reaching a certain part of the kidney tubule. I should like to question whether or not these are effects of alkalosis. I should think, rather, that these effects are those of a large amount of sodium reaching a certain part of the kidney tubule, at which point there is an increased exchange of potassium for sodium.

His finding of increased alkalosis with a phosphate load would suggest exactly this: that there is more phosphate and therefore more cation arriving at this point, and consequently there is a greater exchange of potassium for sodium in total quantity, with a greater depletion of potassium in that particular area.

The other question that I should like to ask him, and I happen to have the advantage of having seen one of his newly submitted papers before publication, is whether or not his animals in which he used nitrate as a loading anion had similar lesions, because those animals, as I remember it, did not develop any alkalosis, and yet they most certainly had acute potassium deficiency.

DR. PHILIP L. CALCAGNO, Buffalo: Several years ago, Dr. Rubin and I studied a group of patients with metabolic alkalosis due to vomiting from pyloric stenosis. These patients also had associated dehydration. We found that these patients had a reduction in the glomerular filtration rate, and with administration of fluid the glomerular filtration rate rose.

We also noticed in calculating the amount of excretion of electrolytes, particularly potassium, that 40% of the potassium filtered was excreted in the urine of these patients, as opposed to, at the time of recovery, approximately 10% of the filtered potassium that was excreted. This meant to us that these patients were excreting a greater quantity of potassium during this metabolic alkalosis phase.

I should like to ask Dr. Holliday whether or not he has studied rats that have prevously had metabolic alkalosis, treated them to return them to a normal state, and then observed the renal tubules? In other words, at what level of metabolic alkalosis can one anticipate irreversible tubular damage?

DR. CHARLES D. COOK, Boston: I should like to bring one more electrolyte into this discussion and ask whether possibly magnesium may be related to these lesions. As I remember, pathological descriptions of magnesium deficiency in the rat were very similar to the lesions described by Dr. Holliday. Necrosis and calcification were characteristic findings.

DR. ROBERT SCHWARTZ, Boston: I don't have any personal data to report, but I should like to call attention to two other bits of data relative to this.

First, in the *Federation Proceedings*, there was a report by Dr. Edward Muntwyler, in which the kidneys of animals which were made potassium deficient were found to have an increase in the activity of glutaminase and carbonic anhydrase. These enzymes are concerned with the excretion of hydrogen ion and ammonia.

Second, Dr. Arnold Relman and Dr. William Schwartz, of Boston, have been interested in the renal lesions in potassium-deficient animals, particularly with reference to the effect of rubidium chloride. They found that the administration of rubidium quickly reverts these lesions which are identical to those shown by Dr. Holliday.

DR. HAROLD E. HARRISON, Baltimore: Dr. Holliday, I should like to know how the phosphate load which you used compared with that which was used by McKay. I had the impression that they used an extraordinarily large phosphate load, far beyond anything that would ordinarily occur in any patient's experience.

DR. MALCOLM A. HOLLIDAY, Fort Bragg, N. C.: The location of the lesion is obviously very pertinent, and we regret we couldn't be more definite about the location. Dr. Gene Oliver has very kindly consented at some later date to dissect out a nephron, and this may give us an answer. Perhaps we may be able to design an experiment that will make it more clear. One of the troubles here is that we postulate two lesions occurring simultaneously, with overlapping of their anatomical location.

As to why sodium acid phosphate sustains a greater alkalosis in animals already made alkalotic than does water, it would, I think, be on the basis of having available more sodium in the tubule, somewhat along the concepts that Dr. Cook alluded to.

Under these conditions, it is more possible, you might say, for potassium and sodium to exchange at the cell membrane site.

With respect to Dr. Cook's comments as to why these animals develop lesions, it is probably not due to the alkalosis per se, but certainly due to some secondary effect, and we have been unable to isolate the effect. This concept is based on the poor correlation between the degree of alkalosis and the severity of the lesions. The presence of sodium in the tubules seems to me to be an unlikely explanation. We had a much different and much more intense lesion with the sodium acid phosphate than we did with sodium bicarbonate; yet we have no reason to believe that there was a difference in sodium concentration in the tubule in these two experiments. The only difference we could see was the presence of phosphate.

The nitrate animals he described were alkalotic at the end of these experiments, and they did have the lesion we described. Again, it is difficult to say whether the lesion developed as a result of the potassium deficiency or as a result of the alkalosis or some process secondary to the latter.

Again we are back at the problem of something happening within the renal cell and presumably also in the muscle cell, in which potassium and sodium concentrations are altered.

I regret to say that I didn't catch Dr. Calcagno's question.

In answer to Dr. Gardner, these lesions are similar to those that are produced by magnesium deficiency. I was unable to compare any directly myself. It is interesting to note that a few years ago in studying magnesium deficiency in animals, we were also able to demonstrate a lowering in the muscle potassium without any rise in serum bicarbonate.

In answer to Dr. Harrison's remarks, our loads were presumably a good bit less than Dr. Oliver's. Dr. Oliver's diets consisted of 10% phosphate, and ours consisted of an isotonic solution of phosphate. I presume the loads were less. It is on that basis that we felt the alkalosis may have, so to speak, sensitized the animal's development of the second lesion.

Effects of Acetazoleamide (Diamox) on Electrolyte Excretion and Body Composition in the Rat. DR. R. LEE WALTON (by invitation) and DR. WILLIAM H. BERGSTROM (by invitation), Syracuse, N. Y.

Acetazoleamide (Diamox), a carbonic anhydrase inhibitor, is known to produce a diuresis of sodium, potassium, and water and a decrease in urinary titratable acidity and ammonia. Continuous administration results in metabolic acidosis and a rapid return of base excretion to normal.

The present study concerns (1) effect on electrolyte excretion of simultaneous administration of desoxycorticosterone acetate (DOCA) and acetazoleamide; (2) effect of continuous acetazoleamide administration on growth rate and on body composition.

Male albino rats were used. Acetazoleamide was given in the drinking water, 666 mg. per liter, providing approximately 50 mg. per kilogram per 24 hours. Twenty-four-hour urines were

collected and analyzed for sodium and potassium. The effects of acetazoleamide were studied in four groups of rats (1) on a normal diet; (2) on a low-sodium diet; (3) pretreated with desoxycorticosterone acetate (Percorten) for two days prior to administration of acetazoleamide; (4) receiving desoxycorticosterone-3-methyl acetate and acetazoleamide simultaneously.

In a fifth group of rats receiving acetazoleamide continuously for 16 days, growth rates were measured and serial serum pH determinations were done. These rats were then analyzed for total body water, sodium, potassium, calcium, chloride; and their bone electrolyte patterns were determined.

In each of the experimental situations described, acetazoleamide caused an initial diuresis of sodium and potassium and marked weight loss followed by a resumption of normal growth rate. Due to rather marked reduction of food intake in rats receiving acetazoleamide, it was necessary to use balance data to demonstrate diuresis of sodium and potassium. Total body analysis indicated no change in any of the constituents measured. Bone sodium and carbonate, however, were significantly decreased. Serum pH measurements demonstrated acidosis throughout the period of study.

DISCUSSION

Dr. Jack Metcoff, Boston: I think that Dr. Bergstrom's very excellent study clearly makes the point he has set out to achieve. Because of limitations of time, I suspect that he was unable to give us a bit more information which might prove of some interest.

First, I am rather curious to know whether the urine was alkaline in the rat on which he did balance studies. Second, I wonder whether he has any particular explanation for the negative sodium balance in control periods of these rats. Third, I wonder if there was any evidence of azotemia or hyponatremia in the sodium-deficient animals.

We have observed that growing sodium-deficient rats supplemented with acetazoleamide get muscle sodium depletion, azotemia, and hyponatremia. The potassium content of muscles remains normal.

As one might anticipate, if there is deficit of one cation arising from diet depletion during growth, then administration of acetazoleamide should induce loss of other cations as well. In growing rats, for example, potassium deficiency with acetazoleamide administration tends to produce a striking deficit of muscle potassium as well as marked depletion of extracellular sodium, with a tendency toward elevated serum pH.

Dr. William M. Wallace, Cleveland: This paper brings out a point which I think has been generally neglected. It has recently become the fashion to imply that acetazoleamide produces an exact replica of such diseases as idiopathic hyperchloremic acidosis. I think that Dr. Bergstrom's data show that this is a dangerous pitfall to get into. Such an enzyme inhibitor produces only a temporary production of an alkaline urine. While the inhibitor is still active, resumption of urine of a normal acid-base pattern is achieved.

Our president today claimed immunity from discussion and implied that enzyme inhibitors produce exact facsimiles of disease. Perhaps he would be willing to drop his immunity and discuss this paper.

Dr. Nathan B. Talbot, Boston: Just one more question. Perhaps Dr. Bergstrom didn't have time to indicate how long, in his experience, it takes the doses of desoxycorticosterone acetate that he used to have their full metabolic effect on these animals.

Dr. William H. Bergstrom, Syracuse, N. Y.: In answer to Dr. Metcoff, we did not, unfortnuately, determine urine pH in the animals. We therefore can make no statement regarding the reaction of the urine at any time.

Numerous previous investigations by others and by one of us have indicated that the pH of the urine changes under continuous acetazoleamide, first to high levels which after the first 24 hours begin to come back to normal and by 36 or 48 hours may be fully as low as those exhibited by normal subjects, even though acetazoleamide is continuously being given, and the diminution of the enzyme can be demonstrated.

The negativity of our control balances has disturbed us very considerably. It might, I suppose, be thought of as an Achilles heel in this experiment. It is a feature we were never able to get rid of. We prefer to give it the elegant name of systematic error. We cannot explain it.

We did not measure NPN. The rats at the conclusion of this study did not show hyponatremia. Our data don't lend themselves to assessing intracellular potassium changes. These rats throughout their period of acetazoleamide treatment had access to a complete synthetic diet; that is, they were not deprived of cations by dietary means.

Dr. Talbot's question escapes me, I am sorry to say. I remember a negative answer to it, but I don't remember the question.

[Dr. Talbot repeated his question: "I was curious to know how long it took for the adrenal steroids to become effective—the time required for maximum effectiveness."]

This we do not have a precise measurement of from our own data. From the data of others, it seems apparent that the steroid preparations of the sort which we gave might be expected to become effective within 24 hours of the time given.

I realize that this is indeed a crucial point and would strongly indicate the desirability of going further in this matter, using an aqueous or intravenous steroid preparation.

Dr. Harold E. Harrison, Baltimore: I shall not stand on presidential immunity. As you noticed, the increased urinary excretion of sodium does tend to disappear with continued acetazoleamide administration. But you will also notice that the animals remain acidotic. The effect of acetazoleamide has not been completely reversed, and the animal has not compensated during this period when his urine sodium begins to diminish. In other words, you still have a chronic acidosis, and, therefore, actually, the disturbed metabolc state has not disappeared, even though sodium loss has diminished after continued administration of this carbonic anhydrase inhibitor.

A Controlled Study of the Influence of Triton WR-1339 Aerosol upon Death Rate and Autopsy Findings Among Premature Infants. Dr. William A. Silverman and Dr. Dorothy H. Andersen, New York.

It has been suggested that premature infants who develop respiratory obstructive signs in the first few days of life may be benefited by an environment which is supersaturated with water. More recently it has been advocated that a solution of 0.125% Triton WR-1339, 5% glycerin, and 2% sodium bicarbonate in distilled water and Alevaire (alkylaryl polyether alcohol detergent) be nebulized to produce a mist for the "treatment . . . of all premature babies." A large experience with this material in animals, tuberculous children, and adults has failed to demonstrate any untoward effects from prolonged inhalation. In vitro experiments and clinical testimonials have called attention to the ability of this detergent solution to thin viscid secretions (bronchiectatic pus, saliva, and amniotic fluid). Since the introduction of Alevaire mist therapy it has been used on an empirical basis widely throughout the United States. The results of a controlled clinical trial have never been published to establish acceptable proof of the efficacy of treatment of premature infants with Alevaire mist. It was the purpose of this study to conduct such a controlled clinical trial.

From May, 1953, through March, 1954, 200 infants were admitted to the premature nursery of the Babies Hospital. These infants were allocated to "Alevaire" and "control" regimens at the time of their admission, as determined by random order. Once assigned to the allotted regimen, the infants remained, without exception or deviation, upon the prescribed course of therapy.

Infants assigned to the "Alevaire group" were placed in Isolette incubators. Alevaire was nebulized by means of oxygen flowing through a Vapojette at the rate of 6 liters per minute. This was administered unchanged until the infant reached the age of 72 hours. Those assigned to the "control group" were placed in Isolette incubators, with oxygen introduced at a rate of 2 liters per minute; relative humidity ranged between 90 and 100%. Oxygen concentrations were measured three times per day, and comparable concentrations (range, 34 to 48%) were obtained in both treated and control incubators. The conditions of the trial were terminated when the infant reached the age of 72 hours.

The treated and control groups were equal (within the limits of random variation) in the following characteristics: total number, sex, color, birthplace, service, birth weight, gestational age, birth rank, maternal age, type of delivery, and stated cause of prematurity. The two groups were treated with comparable doses of prophylactic antibacteria drugs. The infants in the two categories were admitted to the nursery at comparable ages, and deaths in the two groups occurred at equivalent ages, resulting in uniform durations of exposure to risk.

The mist environment created by Alevaire and generated by the Vapojette nebulizer in the Isolette incubator compared favorably with environments created by other nebulizers and incubators. It was shown that comparable blood levels of sulfadiazine were obtained in one test infant who was exposed to a mist obtained from a 5% solution of sulfadiazine in Alevaire generated by two different nebulizer-incubator combinations (Vapojette-Isolette versus Vaponephrin-Armstrong). Also, infants of less than 1,251 gm. birthweight, who received no feedings from admission to the nursery until the age of 72 hours, lost less weight in the Alevaire environment than controls in the 90 to 100% relative humidity environment.

There was no significant difference between the death rates of the two groups, nor was there a difference in the pathological findings among the autopsied infants in the two groups.

From the foregoing findings, it was concluded that the initial weight loss of very small infants was reduced when they were placed in Alevaire mist for the first three days of life. Despite this effect, no therapeutic benefit as reflected by change in death rate or autopsy findings could be demonstrated in a 10-month controlled experience with Alevaire mist administered to premature infants.

DISCUSSION

DR. DAVID T. KARZON, Buffalo: I noted the word bacteremia in the No. 5 and the No. 0, and the 5 was under Alevaire and the 0 under control.

Was bacteremia detected in any of the children who did not die in the Alevaire series, and was there any difference in the bacteremia in the two groups as indicated or suggested here?

DR. SYDNEY S. GELLIS, Boston: I should like to ask why a third group was not instituted, one without mist. It seems to me this would have been vitally important.

DR. JAMES B. AREY, Philadelphia: I should like to congratulate Dr. Sliverman and Dr. Andersen on an excellent study. The results of this study have, I believe, been predicted at times in the past, but only as a result of the present careful study have at least some of these predictions been confirmed.

I should like to ask two questions. First, whether there was any opportunity to study the presence or absence of any disturbance of electrolytes in the infants receiving Alevaire, which might be associated with the presence of the sodium bicarbonate in the Alevaire. In other words, might the deleterious effect which has been demonstrated on the Isolettes also be demonstrated clinically in the patients. Second, was any attempt made to grade the hyaline membranes pathologically either in the control or in the study series?

DR. CLEMENT A. SMITH, Boston: I should like to express my appreciation for this study, because it has proved again the only thing we previously knew about mist—that it decreases body water loss—and has also confirmed what we had previously suspected—that it does not importantly affect pulmonary pathology in the newborn.

I should like to know whether the infants showed any coughing or sneezing. We have observed that adults working around these mixtures notice some evidence of nose and throat irritation. Perhaps Dr. Silverman may have something to say about this.

DR. ALFRED FLORMAN, Long Island, N. Y.: I was interested to see that this experiment with the use of mist terminated at 72 hours, because there is a real danger to the skin if one continues with heavy mist beyond this period. We had the unfortunate experience of having a newborn develop macerated skin and generalized moniliasis secondary to a more prolonged use. I believe it was about the fifth or sixth day after the mist had been started that we first became aware of this problem.

DR. DAVID YI-YUNG HSIA, Boston: I should like to suggest the use of counting rates of respirations as an objective method for evaluating respiratory distress in infants with hyaline membrane disease.

In infants of diabetic mothers, we were impressed by the fact that the degree of respiratory distress could be divided into three types: (1) those with frank hyaline membrane disease, where the rate of respiration would exceed 100 per minute; (2) those with no clinical incidence of respiratory distress, but where the rate of respiration would be elevated to 60 to 80 per minute, which might represent subclinical hyaline membrane disease, and (3) those with normal respiratory rates of 40 per minute during the first 36 to 48 hours of life.

We have observed this same phenomenon in a number of premature infants and found that their respiratory rates also have a tendency to increase without real evidence of clinical hyaline membrane disease. This does not seem to occur with normal full-term infants and infants delivered by Caesarean section.

DR. EDWARD WASSERMAN, New York: We have been studying the action of Triton WR-1339, as well as other surface-activating materials. Two properties of these agents were investigated, one, their ability to reduce surface tension of sputum. Triton WR-1339 alone and Alevaire reduced insignificantly the surface tension of various sputa.

The problem of reduction of viscosity is somewhat more complex. Sputum of low viscosity is less affected and sputum of high viscosity more affected by the addition of surface-active agents.

Material aspirated from the posterior pharynx of premature infants is usually of low viscosity. There is minimal effect, therefore, following administration of Triton WR-1339.

DR. WILLIAM A. SILVERMAN, New York: In reply to the question about the difference in incidence of bacteremia in the two groups, it can only be stated that the instances are too few to permit a statistical judgment. The total incidence of major infection was insignificantly different in the two groups.

Dr. Gellis has asked about the control conditions. The infants in the control group were in incubators at standard operating conditions in which the relative humidity was maintained between 90 and 100%. No nebulized mist was introduced into these incubators. Another trial is planned to follow the present study in which nebulized mist (water) will be compared with standard operating conditions (no aerosol, 90 to 100% relative humidity).

In response to Dr. Arey's question concerning the 2% sodium bicarbonate content of Alevaire, we can only say that although we were concerned, we have no objective observations to report. It should be pointed out that infants who were exposed to this highly alkaline solution for the periods stated experienced a mortality rate that was no higher than in the control group.

To comment on Dr. Arey's remarks about severity, we were interested in the three examples of hyaline membrane formation which were observed in infants who died after the age of 72 hours. Dr. Dorothy Andersen stated that in two of these (one post-"Alevaire," one post-"control") there seemed to be some resolution of the hyaline material. We did not observe coughing or sneezing in the infants; however, the nurses were occasionally so afflicted.

In reply to Dr. Florman, we chose the age of 72 hours as the arbitrary time to discontinue the conditions of the trial because this coincided with our past experience with the age incidence of the hyaline membrane syndrome among premature infants. Any controversy about continuous versus discontinuous administration of this aerosol is partially answered by our experience, which shows no difference in death rate between treated and control groups. Thus, one cannot imply that continuous administration was harmful. A similar argument applies with respect to cessation of "treatment" at 72 hours of age. If this aerosol was saving lives and therapy was stopped too soon, one would have expected the deaths to pile up in the immediate post-treatment period. This was not observed.

Dr. Hsia's comments about objective measures to evaluate clinically the respiratory syndrome interest us a good deal. We have attempted to devise a scheme of grading the degree of retractions and are incorporating this scheme in the study which is currently under way. Respiratory rate will also be included and correlated with outcome and autopsy findings.

Dr. Wasserman's comments about viscosity are gratefully received. There is published evidence by Qualls and co-workers to the effect that the alveolar-capillary transfer of water in the lungs of dogs was influenced by osmotic pressure gradients between alveolus and capillary. Isotonic saline was transferred less rapidly than distilled water. We have found that Alevaire is extremely hypertonic. From this we should like to hazard the prediction that the initial weight loss of infants exposed to water mist will be less than that sustained by those who were exposed to Alevaire mist.

Interference in Tyrosine Metabolism in Phenylpyruvic Oligophrenia. DR. JOSEPH DANCIS and DR. M. EARL BALIS (by invitation), New York.

It has been assumed that patients with phenylpyruvic oligophrenia are blonde because their inability to oxidize phenylalanine to tyrosine results in insufficient tyrosine for melanin formation.

However, this mechanism does not explain the recent clinical observation that a low phenylalanine diet improves melanin formation in phenylketonurics. An alternative hypothesis which could explain both observations is that phenylalanine in high concentrations interferes with the enzymatic conversion of tyrosine to melanin by tyrosinase.

The authors attempted to find evidence for the latter hypothesis by means of an in vitro study using a purified tyrosinase preparation. Under these conditions it was demonstrated that *l*-phenylalanine inhibits the oxidation of tyrosine by tyrosinase as measured by oxygen uptake and by the intensity of pigment formation. The inhibition is stereospecific, and the amount of inhibition is directly related to the level of phenylalanine. It is probably the result of the similarity in structures of the two amino acids (tyrosine is hydroxyphenylalanine).

DISCUSSION

DR. HENRY E. KRETCHMER, New York: I thoroughly enjoyed Dr. Dancis' paper, and we are particularly interested in this problem. We are working with tyrosine metabolism from a different aspect and are particularly interested in the tyrosine oxidation.

I should like to ask Dr. Dancis three questions: (1) whether he incubated phenylalanine with tyrosinase and whether there was any oxygen uptake with that; (2) whether he used any other aromatic amino acids or substituted aromatic amino acids and obtained the same type of inhibition; and (3) whether he feels that this effect of level of phenylalanine in relation to the inhibition of the tyrosinase is more of a substrate effect, rather than a specific phenylalanine effect.

DR. SAMUEL P. BESSMAN, Washington, D. C.: We have done a number of experiments with radioactive phenylalanine, and I was particularly interested in these observations, since the *d* and *l* forms of phenylalanine are, of course, metabolized differently.

I cannot understand why, if *l*-phenylalanine is exerting a specific effect, *dl*-phenylalanine doesn't exert half the effect.

DR. JOSEPH DANCIS, New York: The effect of tyrosinase is specific for the phenol radical. We used a purified tyrosinase and so would not expect an effect on phenylalanine; however, we did not investigate that in the present experiments.

We did not measure the effect of other substituted aromatic amino acids on the tyrosine-tyrosinase reaction.

I'm afraid I did not catch the third question by Dr. Kretchmer.

In response to the second questioner, we compared the inhibitory effect of *l*-phenylalanine with *d*-phenylalanine.

The Syndrome of Patent Ductus Arteriosus with Marked Pulmonary Hypertension: Report of Four Cases and Review of the Literature. DR. PAUL N. YU (by invitation), DR. FRANK W. LOVEJOY JR. (by invitation), DR. HOWARD A. JOOS, DR. ROBERT E. NYE JR. (by invitation), and DR. DAVID C. BEATTY (by invitation), Rochester, N. Y.

Four cases are reported of patent ductus arteriosus with severe pulmonary hypertension. The correct diagnosis was missed clinically in three. All complained of easy fatigue and exertional dyspnea. Generalized cyanosis and clubbing of the extremities were notable in two and visibly more pronounced in the lower extremities of one. Cardiac enlargement and accentuation of P_2 occurred uniformly. A continuous murmur was heard in only one instance. The electrocardiogram of three patients showed right axis deviation and right ventricular hypertrophy; one patient exhibited normal axis and combined ventricular hypertrophy. X-ray studies of three patients uniformly revealed enlargement of the pulmonary artery and right ventricle and accentuation of pulmonary vascular markings. Left ventricular enlargement and intrinsic hilar pulsations were seen in two instances each. Cardiac catheterization of three patients revealed pronounced pulmonary hypertension in all. Two had unsaturated arterial blood, indicating shunt reversal. Pulmonary "capillary" pressure was normal in the single case in which it was measured. Angiocardiography in one case showed simultaneous early filling of pulmonary artery and descending aorta. Postmortem examination of two cases revealed structural abnormality of pulmonary arterioles in each.

Search of the literature reveals 39 cases reported in nine years and permits definition of atypical patent ductus as a recognizable syndrome, clinically and pathologically. Successful

surgical closure of the ductus has been reported in a number of selected cases. The dynamics of flow through the ductus are discussed, and the recognizable peripheral manifestations with flow reversal are emphasized. The pathogenesis of pulmonary hypertension, probably precapillary in these cases, is discussed. The favorable effect of ligation of the ductus in selected cases is cited, emphasizing the need for diagnosis before pulmonary hypertension and irreversible pulmonary vascular disease become severe.

DISCUSSION

DR. LORIN E. AINGER, Salt Lake City: The incidence of pulmonary hypertension in Salt Lake City has disturbed us somewhat. Of the six or seven patients with patent ductus arteriosus who have been catheterized this year, all six or seven have had a considerable degree of pulmonary hypertension. This has led us to catheterize routinely all patients with patent ductus arteriosus before surgery at the present time. At surgery we are also attempting to elicit the surgeon's cooperation in obtaining lung biopsies so that we can see whether or not arteriolar changes are frequent in association with this pulmonary hypertension.

In addition, we have encountered a very high incidence of pulmonary hypertension in association with other congenital cardiovascular defects. We have encountered patients who show a combination of the features of the tetrology of Fallot and the Eisenmenger complex. These patients have a marked degree of pulmonary stenosis in association with a moderate degree of pulmonary hypertension. These children are acyanotic, there being only slight arterial oxygen desaturation; they do not suffer from exercise intolerance, and they have an ECG which frequently shows an incomplete right branch block instead of right ventricular hypertrophy.

In connection with angiocardiography in the presence of pulmonary hypertension, I should like to mention that we feel angiocardiography is contraindicated because of two deaths which have occurred following angiocardiography in two cases of primary pulmonary hypertension.

We do not know the reason for our high incidence of pulmonary hypertension, but we suspect that the altitude may have something to do with it. Blount, in Denver, has encountered a similar incidence of pulmonary hypertension, and pulmonary hypertension also is said to be of very frequent occurrence in Mexico City, which has an altitude of about 6,000 ft.

DR. FOWLER, New Orleans: We have recently been interested in this syndrome of pulmonary hypertension with patent ductus arteriosus and have reviewed our experience with it, most of it in the past year and a half, but with some of the cases going back about five years. We have 15 cases, which range in age from 6 months to 11 years.

We have divided these up into 10 cases with severe pulmonary hypertension, by which we mean those in whom the systemic pressure is equivalent to the pulmonary pressure, and 5 cases with somewhat less severe pulmonary hypertension; but in 3 of these the systolic pressure was above 75 and in the other 2, above 50.

I don't know how this fits in with the concept which has just been mentioned of altitude having an effect, since the average altitude in New Orleans is 5 ft. above sea level.

In general, we think we have been able to make a correlation, as far as the clinical findings are concerned, with the degree of pulmonary hypertension. The type in which pulmonary and systemic pressures are equal usually shows a diffuse rough precordial systolic murmur which is not very characteristic of anything and frequently may be duplicated by the murmurs of septal defects or other congenital lesions.

In the second group, which had considerable pulmonary hypertension but not quite as high as the systemic level, there was usually a continuous murmur but rather an atypical kind, the type which is debatable.

In the third group, which had definite pulmonary hypertension but, nevertheless, a considerable difference between systemic pressure and pulmonary pressure, the murmur was usually continuous and typical in nature.

In those children with severe pulmonary hypertension, the usual findings related to a wide peripheral pulse pressure were not present. The ECG picture was similar to that described by Dr. Joos. In those with severe pulmonary hypertension, we have seen only right ventricular hypertrophy, whereas in those with a little less pulmonary hypertension, we may see combined ventricular hypertrophy.

There is frequent fluoroscopic evidence of left atrial enlargement. Our catheterization studies usually reveal a small left-to-right shunt, sometimes rather equivocal, and in most instances the diagnosis was actually made by passing the catheter through the ductus.

In one case in whom we were unable to get the catheter beyond the right ventricle, the diagnosis was confirmed by a demonstration of unsaturation of arterial blood in the femoral artery during exercise while the child was breathing 100% oxygen, while at the same time blood from the right brachial artery was fully saturated.

Our surgical results have been somewhat disappointing. Some patients have had unfortunate accidents, which probably are related to the fact that these children are quite fragile and do not tolerate any sort of procedures very well. We have had several, however, which have definitely been improved, and some improved more gradually, as pointed out by Dr. Joos.

DR. HOWARD A. JOOS, Rochester, N. Y.: I am very sorry the discussion has to be cut off, because these experiences are of very great interest to me.

Although our series is not large, we have had no fatalities following angiocardiograms in patients with pulmonary hypertension. In the present patient, using the motion picture angiocardiographic technique, we were fortunate in being able to demonstrate spurts of contrast substance coming from the ductus and traveling down the descending aorta, even though the ductus itself was not visualized.

Protein Clearances in Children with Nephrosis and Chronic Nephritis. DR. WALLACE W. MCCRORY, DR. CHARLOTTE LIU (by invitation), and DR. MILTON RAPOPORT, Philadelphia.

The mechanism responsible for proteinuria in children with nephrosis is as yet unclear. The quantitative study of the clearance rates of the various serum protein fractions in children with renal disease could provide valuable information on this important problem. We have begun such studies employing filter-paper electrophoresis for the separation of serum and urine proteins. Values we have obtained for the separate fractions (albumin, alpha 1 and 2 globulins, beta globulins, and gamma globulin) in serum and urine by this technique are in agreement with values reported by others in similar studies using the Tiselius apparatus. Twenty-four-hour urine collections have been obtained, and protein fraction clearances have been calculated. Glomerular filtration rate has been measured by the endogenous creatinine clearance (Ccr). Assuming the Ccr is a measure of the permeability of the glomerulus to water, the ratio of protein clearance : Ccr can be calculated. This ratio provides a means of estimating the minimal permeability of the glomerular membrane to proteins in relation to permeability to water. Data obtained for the various protein fraction clearance ratios in eight children with nephrosis support the hypothesis that molecular size of proteins influences their passage through the glomerulus in this disease. The protein fraction ratios are inversely proportional to molecular size of proteins comprising the fractions. Studies on three patients with terminal nephritis who began with the nephrotic syndrome revealed no such "selective" permeability differences between values for protein fraction clearances. All values were similar in these subjects. Studies have been carried out before and after diuresis induced by steroid therapy. Increases in protein excretion in patients maintained on steroid therapy have been observed that are not associated with changes in glomerular permeability. The implication of these findings on the pathological differentiation of nephrosis and nephritis will be discussed.

DISCUSSION

DR. WALTER HEYMANN, Cleveland: We have done some investigations along similar lines, but I think Dr. McCrory has gone about it in a more delicate way.

We were stimulated to do that by a 15- or 16-year-old publication of Blackman, who believed that the excretion of large amounts of globulin would possibly indicate a malignant course of the nephrotic disease.

Our results are in line with those presented by Dr. McCrory. I remember one nephrotic child in terminal renal failure whose electrophoretic pattern was almost identical with the one of the serum. We also have found in nine children studied before and during diuresis induced by hormones that there was no appreciable effect on the albumin-globulin ratio in the urine during diuresis.

What I should like to ask Dr. McCrory is this: In regard to the Blackman publication, we found that the four children that died in renal failure all had high globulin excretions in excess of 45% of the total protein output for 24 hours; but two benign nephrotics also had a high globulin excretion.

When we plotted the 24-hour excretion of globulin, however, the picture looked different in that only the children that died in renal failure had more than 2 gm. of globulin excreted per 24 hours, a figure which was not reached thus far, at least, by over 12 benign nephrotics in whom these studies were done repeatedly.

DR. DAVID GITLIN, Boston: When I first heard this paper, I had a number of questions I was going to ask, but Dr. McCrory very nearly foiled me by answering them himself at the very end, namely, the difficulties in using electrophoresis as a precise tool. It is not a precise tool; it is a very crude tool. But for a study such as this, it can be a very useful tool.

I was very happy to hear him mention the fact that the individual peaks are very heterogeneous with respect to molecular size, and it would be very difficult to draw any definite conclusions. Another example is acid glycoprotein having a molecular weight of 40,000 appearing in tremendous quantities in the urine of nephrotic patients, and yet it cannot easily be found on the electrophoretic pattern of the serum.

The only question I ask Dr. McCrory for point of information is whether or not he measured the total serum proteins and the electrophoretic distribution of these serum proteins in patients with terminal nephritis as compared to nephrosis. In our experience, and I believe Dr. Heymann has had the same experience, in nephritis, the serum proteins rise toward the end of the disease, and children with chronic terminal nephritis tend to have higher serum proteins than children with nephrosis and nephrotic syndrome.

DR. WALLACE W. MCCRORY, Philadelphia: I can answer Dr. Heymann in stating that we have also had reason to doubt the value of the urinary protein albumin-globulin ratio as an index of what the course of the disease may be. This is particularly true where rates of excretion of protein are low in these patients. In the children that have the classic nephrotic syndrome, we usually find urinary globulins accounting for more than 50 or 60% of the total urine protein if the total daily output is 1 gm. or less. I think this clearly reflects the need for information about what the tubular mechanisms are of protein reabsorption and whether or not thresholds exist for these functions.

In answer to Dr. Gitlin, our biggest problem in trying to pick two groups was to get any agreement about what the groups would consist of. The chronic group I have shown consisted of two children who had terminal renal failure after three-year histories of the nephrotic syndrome but who no longer had edema. The other child with a total serum protein of 8 gm. really had a subacute nephritis, and the whole course lasted only three months. He fitted best in his clearance values with the two children who had reached the same stage in three years. I should agree that our experience is that the total serum protein values are usually in the range of normal in patients with terminal nephritis. Thank you.

Investigations into the Site of Complement Loss in Acute Human and Experimental Glomerulonephritis and the Nephrotic Syndrome. DR. KURT LANGE and DR. EUGENE J. WENK, New York.

The lowering of serum complement levels in acute and subacute glomerulonephritis and the nephrotic syndrome has been firmly established as a constant feature of the disease. Definite proof has been lacking that lowering of complement is due to use of complement or some of its components in an antigen-antibody reaction. It has been suggested that complement may be lost into the urine with the proteins or may be insufficiently produced.

To investigate these points, sera and urines of patients with severe proteinurias were analyzed for the individual components of complement. In spite of the severe proteinuria, complement levels are normal in amyloidosis of the kidney, Kimmelstiel-Wilson syndrome, and toxemia of pregnancy.

Urines of patients with severe proteinuria resulting from nephritis, nephrosis, amyloidosis, and Kimmelstiel-Wilson syndrome were examined quantitatively for components of complement. Varying amounts of different complement components were excreted in all these cases, irrespective of serum complement levels. In none of them was the excretion large enough to explain the lowering of serum complement, when present. The return of serum complement levels to normal was only rarely accompanied by a decrease in excretion of complement components in the urine. The degree of proteinuria did not determine which component was excreted or to what extent.

When sera of nephrotics and nephritics were analyzed for individual complement components, C'2 was always the limiting factor resulting in lowered complement levels, and C'4 was also depressed in most instances.

During healing, the C'2 value ascended but remained the limiting factor until healing was complete and all complement components returned to normal.

To prove the direct absorption of complement by the antigen-antibody reaction taking place in the kidney, isolated rat kidneys with ligated ureters were perfused by means of a recirculator device with freshly prepared rat serum. When nephrotoxic anti-rat-kidney rabbit sera were added to the perfusate in minute amounts, they did not influence the complement content of the perfusate before circulation through the kidney. Immediately upon one passage through the kidney, large amounts of complement disappeared from the perfusate. The amounts of complement removed were in direct proportion to the amount of nephrotoxic serum added. The components of complement which became the limiting factors of complement activity in this antigen-antibody reaction were identified as C'2 and, to a lesser extent, C'4. Cortisone added to the perfusate on this system did not alter the reaction. When nephrotoxic anti-rat-kidney duck sera instead of nephrotoxic rabbit sera were added to the perfusing rat serum, lowering of complement did not occur. Liver was also perfused with these sera, and it was found that complement is also removed by it, but to a much lesser extent than by kidney. The pattern of absorption of individual complement components in the perfusion experiments closely simulated the pattern of depression of complement components found in human cases of acute glomerulonephritis and the nephrotic syndrome, namely, a removal of predominantly C'2 and, to a lesser extent, C'4. This pattern is typical for complement removal by immune precipitates.

DISCUSSION

DR. WALTER HEYMANN, Cleveland: I should like to congratulate Dr. Lange for his very impressive investigations.

As to the first part, I should like to ask him one question. He agrees in his results with the observations made by Ecker and Seifter that C'2 and C'4 are found in the urine of nephrotics. I should like to know whether Dr. Lange believes with Ecker and Seifter that these amounts would be large enough to account for the depletion in the plasma of nephrotic children.

How do the figures that Dr. Lange obtained in the urine compare with those published by Ecker and Seifter?

As to the very impressive and elegant perfusion experiment, I certainly should agree with the interpretation given by Dr. Lange that they most probably show that the antigen reaction in the kidney has led to the complement depletion in the perfusing serum; but one has to realize that the nephrotoxic sera contain multiple antibodies. They contain not only antikidney antibodies, but they do contain antibodies against rat plasma, rat red blood cells, interstitial tissues, and so forth. This has been shown by several investigators.

It thus is very well possible that the depletion of complement in the perfusing serum has been produced by other than renal antibodies.

It would be interesting to adsorb the antikidney serum with rat-kidney extracts. If then no complement depletion in the perfusing serum would occur, it would prove the point that what Dr. Lange saw before was due to the antikidney antibody-antigen reaction that took place in the kidney.

DR. HENRY L. BARNETT, New York: I believe that determining the significance of changes in the concentration of complement in nephrosis is of tremendous importance. If Dr. Lange is right in his interpretation that the concentration of complement in serum is a manifestation of the activity of this disease, it is an extremely important step forward in our understanding of this disease, and also it would be useful in directing treatment. I believe the problem has to be looked at very critically.

I was glad that in his presentation Dr. Lange inserted the word "almost" in the statement that the low complement was almost a constant feature, because although in general we have found the same thing in our own laboratory, we have undoubted instances of children with active disease whose serum complement concentrations were within the normal range.

Despite the fact that complement is not low in other diseases with equal proteinuria, I should still question whether or not we can be certain that urinary loss is or is not respsonsible for the

low serum complement in nephrosis, particularly when Dr. Lange finds that as much as 14% of the calculated total complement of the body can be lost in the urine in one day. The concentration of any substance in plasma will ultimately depend on the rate of removal from plasma and the rate of addition. Thus far, the rate of addition of complement to plasma in patients with nephrosis has not been measured. The fact that it can be increased very rapidly under acute stimulation in other children does not tell us very much about what its rate of addition would be during chronic loss in patients with nephrosis.

Finally, I should like to report one observation: during diuresis induced with dextran, we have observed fairly constantly a fall in serum complement. Had we observed a rise, as occurs with diureses induced with cortisone, it would have thrown considerable doubt, I think, on Dr. Lange's hypothesis.

DR. RALPH WEDGWOOD, Cleveland: I agree with Dr. Lange's hypothesis that complement loss in the urine is not the cause of the hypocomplementemia found in nephrosis and certain other collagen diseases. However, the proof of this hypothesis by the measurement of complement components in the urine is a hazardous business. The value obtained for the measurement of a single component, using standard reagents, depends upon the concentration of all the other components in the system at the time the measurement is made; it is not a pure measurement of one component, but an estimate of the activity of one component as it relates to all the other components in a nonstoichiometric system. Thus, when one makes a measurement of this nature, one has to take into account what is happening to all the other components in the system, in the unknown sample, and in the reagents themselves.

It is also a common experience to find, when measuring individual components of complement, and in particular the "limiting component," that the limiting component titer as measured by the reagents is appreciably higher than the total complement titer of the original sample. Such a finding suggests that the sum of the parts adds up to more than the whole and makes mathematical interpretation difficult. In computing urinary complement losses, one would also like to know how long complement components can survive in urine at 37 C.; how long complement can survive as it is exposed to concentration and dilution in the kidney and is left in the bladder; whether the survival varies in different protein concentrations in the urine, such as occur during diuresis in many nephrotics, and whether the ionically dilute urine that may occur during diuresis inactivates the components in a different manner than the urine prior to diuresis.

I wonder whether these factors might not preclude the mathematical computation of urinary complement losses. We also have found, in a few urines that we have tested, high complement component levels in the urine during the edematous stage of the nephrotic syndrome and very low levels during diuresis. But these titers were concentrations, and I have hesitated to calculate total complement excretion until I know more about the survival of complement in the urine and the dynamics of measurement of components with the reagents available today.

DR. LEWIS THOMAS, Minneapolis: The assumption that a diminution in the level of complement in the blood during the course of a disease is due to an antigen-antibody interaction is an attractive hypothesis, but it should be emphasized that it is only a hypothesis. It is possible to reproduce the situation in experimental animals, by simultaneous exposure to large amounts of antigen and antibody, but it is very difficult to do so, and such experiments are not easy to interpret in terms of human disease, especially diseases as obscure as nephritis and nephrosis.

It is difficult to support the assumption that complement fixation occurs in vivo by experiments involving perfusion of kidney tissue with serum. Serum does not exist in vivo, and, indeed, the question has been raised unanswered for many years as to whether complement itself exists in vivo.

I should like to ask whether attempts were made to demonstrate disappearance of complement from perfused whole blood, with or without anticoagulants. I'm aware of the difficulties involved in estimating complement in this situation, but I wonder if there are any data on the point.

DR. KURT LANGE, New York: I think that the answer to many of the questions brought up in the discussion could have been obviated if the time limit on the paper would not have prevented me from bringing up certain facts.

As far as Dr. Heymann's question concerning the work of Ecker and Seifter is concerned, we wish to state that our results are very similar in direction to theirs. In their publication, however, they did not give any information about the age and the body weight of the patients

or the 24-hour amounts of urine. Arbitrarily assuming the weight of the children to be 50 lb. (22.7 kg.), the results of these authors are similar to ours, and assuming reasonably normal figures for body weight and 24-hour amounts of urine, their values would mean that less than 10% of complement is lost into the urine per day, figuring on the predominant component of complement excreted. As far as the second question of Dr. Heymann is concerned, we have in every experiment set aside a sample of the rat serum together with an aliquot of anti-rat-kidney rabbit serum for the length of time which the experiment lasted, in order to see if there was any anticomplementary action of the antiserum when standing at room temperature. Otherwise, all samples were immediately placed in an ice bath. The sera used did not show any major degree of anticomplementary action. Those which did show considerable anticomplementary effects were excluded from the tabulations.

Like Dr. Barnett, we have also seen some cases with the nephrotic snydrome in which the serum complement level was in the lower range of normal, and I think that this is only natural, for if the antigen-antibody reaction is relatively small in extent, then the normal body production of complement may still suffice to keep the level within the range of normal.

I am very happy about Dr. Barnett's results using dextran to induce temporary diuresis in nephrotics. Since complement does not rise in this instance in contrast to spontaneous diuresis or diuresis induced by corticotropin (ACTH) or cortisone, it shows that the diuresis in itself is not the factor producing the rise in complement. We have done experiments to evaluate the recovery of complement from urine. When guinea pig complement was added to urine, losses up to 50% were common when the original method of Seifter and Ecker was used, but when one modifies it, shortening the time of dialysis to four hours and using a mechanical stirrer in the dialysis bag, one can get recoveries from urine of better than 95%. All urine specimens were freshly voided and put on ice in order to avoid loss of complement activity by standing at room temperature. We therefore feel fairly safe in stating that there was not too much loss of complement component activity in these urine specimens. We have calculated our 24-hour amounts on the basis of the one specimen examined multiplied by the 24-hour amount. This procedure is subject to certain criticism, but we did not feel that letting parts of the urine stand for 24-hours would be less objectionable.

As far as Dr. Thomas's question is concerned, we can state that we have tried to use whole blood. The procedure, however, then becomes more complicated, since one cannot use heparin to prevent the blood from clotting; for heparin removes component C'3 from complement, thus inactivating the whole complex. This may be, by the way, the mechanism by which intensive heparinization alleviates experimental nephritis. It may reduce the available complement which is necessary in the antigen-antibody reaction to produce cell destruction and may thus prevent the nephritis from developing to the full. With citrated blood, the results were not different from when serum was used, and we reverted, therefore, to serum itself to avoid unnecessary complications.

Corticosterone Metabolism in Children. DR. J. FREDERICK EAGLE (by invitation), Buffalo.

The paradox that children excrete minimal amounts of urinary 17-ketosteroids in spite of clinically adequate adrenal function is unexplained. Since Compound F (hydrocortisone) is generally considered to be the major adrenal source of 17-ketosteroids, a possible explanation of the low values found in children could be that Compound F is not the principal steroid secreted by the adrenals of such persons. A possible substitute might be Compound B (corticosterone). It is an adrenal secretory product which has been isolated from the adrenal-vein blood of man, has all the life-sustaining properties of Compound F, and is not a precursor of 17-ketosteroids.

Chromatographic studies of the urinary steroids of premature infants suggested that Compound B, rather than Compound F, might be the major adrenal steroid secreted by them. These chromatographic results have been further tested by comparing the amounts of urinary metabolites of Compound B (Pettenkofer chromogens) to the amounts of urinary metabolites of Compound F (17-ketosteroids or Zimmerman chromogens), the P : Z ratio. This ratio has been determined for normal premature infants, premature infants given corticotropin (ACTH) and cortisone, and sick and well children of various ages. In normal adult females, the mean P : Z ratio is reported to be 0.35. In premature infants, the ratio was found to be almost three times as great, 0.85, suggesting that the adrenal of the premature secretes considerably more Com-

pound B than Compound F. The data on older children are not as homogeneous as those obtained from prematures, but suggest that Compound B is the principal steroid secreted by many children.

These results raise questions concerning the use of corticotropin in children. If the anti-inflammatory effects of Compound F are desired, it would appear more rational to administer Compound F than to use corticotropin in those patients in whom the major effect of adrenal stimulation would be increased secretion of Compound B.

DISCUSSION

DR. ALFRED M. BONGIOVANNI, Baltimore: Dr. Eagle has presented some very interesting data, and his speculations may be extremely important.

It may, in fact, be true that children are producing more Compound B, and more definitive evidence of this should be sought. However, I should like to make a few points. One has to do with the Pettenkofer reaction, which was described by Dr. Gallagher and co-workers as being a good measure of dehydroepiandrosterone. Its specificity is open to question, as has been indicated by Dr. Eagle. In attempting to quantitate steroids measured by this reaction, it would be ideal to use as a standard a compound which is believed to be similar to the one being estimated. This is not practicable of course. But if the coefficient extinctions of two different compounds differed widely with this reaction, one could not determine accurately the amounts of the "unknown." Furthermore, we have observed markedly increased quantities of Pettenkofer-reacting material in the urine of patients with the adrenogenital syndrome, in which disease it is presently presumed that Compounds E or F are not produced in normal quantities. Probably Compound B is also somewhat deficient, since it has many of the properties of E and F, and if present in large amount should effectively suppress the disease, as does the exogenous administration of cortisone.

DR. ROBERT KLEIN, Pittsburgh: I want to congratulate Dr. Eagle on this very nice piece of work, and I wonder if he would consider the other possibility that the gland is putting out the same hormone in each case but the metabolism of the hormone is different in younger children from what it is in the older child.

DR. ROBERT S. ELY, Salt Lake City: I should like to join the two previous discussers in saying that this is a very interesting paper, but I should like to suggest that a bit of caution be applied to the interpretation of these data.

We don't know very much about the metabolism of these hormones, and present techniques for evaluating or measuring them are not the very best, as we don't have really sensitive reliable direct measurements. As Dr. Bongiovanni has said, the Pettenkofer reaction is a specific one, but I think the nature of the precursors of these urinary metabolites is difficult to interpret on the basis of the change in ratios between the Pettenkofer reaction and the Zimmerman reaction.

The 17-ketosteroid excretion in the adolescent rises rather markedly, so one might well expect to have a change in the earlier ages, as compared with the adolescent or adult.

The available evidence other than that presented here on Compound B in the blood, in the adrenal veins, and in the adrenal cortex itself would indicate that the ratio of Compound B to F is a rather small one, albeit there is some controversy among people using the same techniques—paper chromatography, for example. Different laboratories disagree as to what the exact ratio is of these two substances, but the over-all serum values of B in children do not differ from those in adults.

DR. VINCENT C. KELLEY, Salt Lake City: One thing I should like to point out is that when one measures excretion of steroids, he should remember that this reflects the influence of many factors other than the secretion of steroids by the adrenal. We have considerable data, both on blood levels and on urinary excretion of steroids, and the two do not correlate very well. I should warn strongly against accepting data on the excretion of steroids as indicating too much about the status of adrenocortical function.

I cannot agree completely with Dr. Eagle's interpretation that perhaps we should always use F instead of corticotropin in therapy. We are not at all sure that the effect we want always is that of F or E. It may be that of one of the other adrenal hormones.

In addition, other data with which I am familiar indicate that there usually isn't a great deal of change in the ratio of corticosterone to Compound F in the blood in response to corticotropin

stimulation. There are some interesting data which indicate that in the pregnant woman at term there are usually tremendous levels of F, but in certain abnormal pregnancies the ratio is reversed, and the B is greatly increased as compared with the increase in F. Apparently considerable variation may occur in the relative amounts of different steroids produced by the adrenal cortex in response to stimulation.

DR. C. N. H. LONG, New Haven, Conn.: I should like to add just one word to what the last speaker said. Nowadays, a great deal of emphasis is being placed on the urinary excretion of steroids as the true reflection of the secretion of the gland. Our experience would certainly lead us to believe that you have to be careful in making such conclusions, since the urinary pattern is not necessarily an accurate reflection of the happenings in the gland itself.

DR. NATHAN B. TALBOT, Boston: In line with the comments concerning the physiologic significance of urinary steroid measurements, one of the factors of some importance in this connection is the procedure used for extracting material from the urine, particularly the question of hydrolysis.

I wonder whether the present workers were measuring the total urinary material or just the free unconjugated material. In the latter connection, studies made in our laboratories of the urinary output of free corticosteroids would suggest that the infant is at least as well equipped to produce Compound-E-and F-like materials under conditions of stress as the adult. This would have the implication, if true, that there are very few occasions on which the administration of adrenal steroids or corticotropin to infants is physiologically indicated.

DR. J. FREDERICK EAGLE, Buffalo: A number of the discussers have questioned the validity of evaluating adrenal secretion by measuring metabolites in the urine, and I should agree that a lot can happen between the time that the gland secretes a hormone and the hormone metabolites appear in the urine. Changes in the pattern of steroids appearing in the urine might be due to changes in the intermediate metabolism or altered function of the kidney, in addition to changes in production. Since this altered pattern of steroid excretion can be duplicated by altering exogenous steroid intake, we have felt that the latter alternative was the most attractive.

Insofar as the specificity of the Pettenkofer reaction is concerned, it measures dehydroepiandrosterone and four other as yet unidentified steroids, called PC-1, PC-2, PC-3, and PC-4, numbered in order of increasing polarity on paper chromatograms. The first three Pettenkofer chromogens appear in increased quantities in the urine after corticosterone administration, whereas dehydroepiandrosterone and PC-4 do not. However, and this may answer Dr. Talbot's question, our technique of hydrolysis with strong acid and heat tends to destroy a large percentage, possibly 60%, of dehydroepiandrosterone, thereby decreasing the effect of a steroid which is not a metabolite of corticosterone.

More work will have to be done to determine the effect of corticotropin on this steroid pattern. It has been our experience that corticotropin in the very young children and prematures increases the Pettenkofer: Zimmerman ratio. However, these were short-term experiments where corticotropin was given for only two days. I should like to call your attention to a paper which was presented in Atlantic City early this week by Kass, Hechter, Macchi, and Mou, (*J. Clin. Invest.* **33**:947, 1954). Corticotropin was administered to rabbits, who normally secrete only Compound B. After 24 hours of corticotropin, the amount of B secreted was increased. After one week of corticotropin, there were equal parts of B and F in adrenal-vein blood. After one month of corticotropin, four times as much F as B was found, demonstrating that long-term administration of corticotropin will change the steroid pattern in rabbits at least, and suggesting that similar changes may occur in humans. The nature of this change, however, remains to be determined.

Concentration Gradient of Plasma Neutral Ketosteroids Between Fetal and Maternal Circulations. DR. LYTT I. GARDNER and DR. R. LEE WALTON, Syracuse, N. Y.

Previous observations by the author and his colleagues have indicated that full-term newborn infants have plasma concentrations of neutral ketosteroids which may range above adult values and which fall precipitously during the first week of life. Are these plasma neutral ketosteroids maternal in origin (mother's adrenal cortex or ovary), or are they being produced by some endocrine tissue in the fetal circulation (fetal adrenal cortex or placenta)? The following study was made in an effort to provide at least a partial answer to this question.

With the assistance of Dr. William Ellis and Dr. Edward C. Hughes, blood samples were obtained from healthy mothers just before delivery and from the umbilical cord when it was cut. The samples were as nearly simultaneous as circumstances would permit. Plasma neutral ketosteroids were determined on 8 ml. specimens by a previously described method (*J. Clin. Endocrinol.* **13**:941, 1953). The results clearly show an increase of neutral ketosteroid concentration in the cord plasma over the mother's peripheral plasma. This finding argues against the maternal adrenal cortex or ovary as sources of plasma neutral ketosteroids in the newborn infant and suggests that the fetal adrenal cortex and/or placenta are responsible.

Evidence was presented which supports the concept that the inner cortex of the fetal adrenal is maintained by the fetal pituitary. It was hypothesized that placental estrogen causes discharge of luteinizing hormone (LH) from the fetal hypophysis, the estrogen having its effect mediated through the neurohypophysis. The LH in turn maintains the internal cortex of the fetal adrenal. Withdrawal of the source of estrogens as a result of birth results in a falling-off of pituitary stimulation by estrogen and in a reduction of LH production. As a result, there is degeneration of the internal cortex of the fetal adrenal.

DISCUSSION

DR. ALFRED M. BONGIOVANNI, Baltimore: Dr. Gardner's theory is interesting. He has cited Klein's work, indicating the absence of corticoids in the circulating blood of the newborn. I see from Dr. Klein's abstract of a paper "read by title" that he finds respectable quantities corticoids among the conjugates in the newborn, which are, if anything, higher than those in the adult. Hence, they seem actually to be present, but unmeasurable by previous techniques. Many mens from patients with this condition to Dr. Janet McArthur, in Boston, who reports that she finds none.

Regarding the possible importance of LH in the adrenogenital syndrome, we have sent specimens from patients with this condition to Dr. Janet McArthur, in Boston, who reports that she finds none.

DR. NATHAN B. TALBOT, Boston: I should like to ask Dr. Gardner if he can solve a problem raised by his thesis. This is in connection with observations which are available on a very interesting group of boys who, at an early age, show striking evidences of spontaneous sex precosity, characterized by massive development of the interstitial cells of Leydig, but no spermatic tubule development, no adrenocortical hyperplasia, and essentially no increase in 17-ketosteroid output.

LH and ICSH are presumed to be synonomous, for LH signifies luteinizing hormone and applies to the ovaries of females, while ICSH is the term applied to the male and indicates interstitial-cell stimulating hormone. Precocious ICSH production appears to be responsible for this syndrome in small boys. If this is so, then why don't we see adrenocortical hyperplasia and increased 17-ketosteroid excretion in these patients?

DR. ROBERT KLEIN, Pittsburgh: I think Dr. Gardner has added another large segment to our knowledge. I had not intended to comment, because I am very much impressed by his speculation. However, I seem to be implicated in this by Dr. Bongiovanni.

The conjugated corticoids are slightly high in a newborn baby. I think, however, this fits with other concepts we have. These represent products ready for excretion. We will show that the conjugated corticoids, after administration of cortisone, for instance, linger in the blood longer than the free. We feel that the conjugated corticoids in the newborn represent hormones made perhaps in the placenta which have been conjugated and which will be excreted.

I would emotionally prefer, because I think the corticoids disappear at about the same rate as the ketosteroids, that the ketosteroids be made in the placenta as well as the corticoids.

DR. J. FREDERICK EAGLE, Buffalo: Measurements of corticoids by means of the Porter-Silber reaction or the eosinophile response determine only 17-hydroxylated steroids, and it is from such measurements that it has been concluded that corticoid production is low during the first week of life. Corticoids measured by means of reducing methods, by the liberation of formaldehyde, or bioassay, have failed to reveal low values during the first week of life, and I suspect that the reason for this is that the newborn maintains adrenal sufficiency by secreting Compound B, a compound whose metabolites are not measured by the first two methods.

Secondly, I think that the weak point in Dr. Gardner's ingenious hypothesis lies in his assumption that the adrenal gland secretes 17-ketosteroids per se, an assumption for which I am unaware of any good evidence. It would appear to me that 17-ketosteroids are metabolic end products of 17-hydroxylated steroids, either active hormones or precursors of active hormones or both.

DR. CHARLES D. MAY, Iowa City: Seeking guidance from other specialties in the society, my query was prompted by Dr. Kelley's comments upon Dr. Eagle's paper, in which he asked us to bear in mind certain skepticism concerning the implication of urinary excretion.

I can understand Dr. Kelley's enthusiasm for the plasma level determination, having moved out to Utah and having Dr. Sayers' and Dr. Samuels' techniques made available to him.

I should like to ask, with perhaps the guidance of Dr. Long, whether skepticism might not be encouraged regarding the implications of plasma level. Truth might emerge from either source, and in neither case need we be overwhelmed by the suggestive evidence. I should like very much to know some of the imperfections in this newer technique, which, because it is newer, is apt to be more impressive.

DR. JOHN J. OSBORN, New York: A short comment again from a nonendocrinologist.

I am just interested in the evidence presented; as I understand it, a good deal of it has to do with the levels of steroids in the infant cord blood being higher than those of the mother's blood, and therefore these steroids must come from the infant. Yet this does not necessarily follow, for in the cases of many types of antibodies which we know are only formed by the mother, the circulating level in the newborn infant may very often be higher than in the maternal blood.

DR. VINCENT KELLEY, Salt Lake City: I didn't mean to imply, as Dr. May seems to have interpreted my previous remarks, that the plasma levels of 17-hydroxycorticosteroids which we measure are necessarily the last word in determining state of excretory activity of the adrenal cortex. As a matter of fact, in our last several papers, I think we have very clearly indicated that we entertain great skepticism as to whether the plasma levels measured exactly reflect adrenal function.

We feel that by a combination of urinary and plasma steroid measurements we get more information and that we shall get a great deal more when we have techniques to measure the entire spectrum of adrenal steroids. At the present time one could measure plasma and urinary 17-hydroxycorticosteroids, Compound F, corticosterone, 17-ketosteroids, total corticosteroids, and conjugated corticosteroids by established techniques. Several additional techniques will have to be developed before anyone will be in a position to evaluate completely adrenal cortex function.

DR. LYTT I. GARDNER, Syracuse, N. Y.: In answer to Dr. Bongiovanni's question concerning corticoids, I shall leave them to Dr. Klein in the next paper. As for LH not being found in the urine of patients with congenital adrenal hyperplasia, I think that it has been observed that the cell types of the normal fetal reticularis and of the hyperplastic zone in congenital adrenal hyperplasia appear to be fundamentally different. Sam Blackman made these observations, I believe (*Bull. Johns Hopkins Hosp.* **78**:180, 1946). I did not intend to imply that the hypothesized LH mechanism for the normal fetal inner zone was also an etiologic mechanism in congenital adrenal hyperplasia.

As for Dr. Talbot's question, I can offer no explanation for the failure of the patient with Leydig-cell precocity to produce 17-ketosteroids.

Relating to his comment concerning the urinary 17-ketosteroids of the newborn infant, I believe that Dr. Charles Read, who is in the audience, some years ago measured these steroids in the newborn, and as I recall his figures, found that although they were quite low in 24-hour excretion in the newborn, there was a clear and distinct fall in the first week of life. I attributed this general lowering of urine 17-ketosteroid concentration to the known "relative inability" of the newborn kidney to function as compared with the adult.

As for Dr. Klein's comment concerning the placenta, I am in complete agreement. We are entirely unable to exclude placenta as a direct producer of these substances. I believe the most fruitful next approach will be placental perfusion to see if it will be possible to produce the substances in that fashion.

As for Dr. Eagle's comment, I think we will only find out whether or not the fetal adrenal makes 17-ketosteroids by proceeding with experiments such as placental perfusion.

Regarding Dr. May's comment about the imperfections of plasma methods. I think that Dr. Klein, Dr. Kelley, Dr. Bongiovanni, and all the rest of us will agree that we are dealing with an extremely demanding chemical technique. All of us are wondering about the relationship of bound steroids in plasma to free steroids.

As for Dr. Osborn's comment concerning the possibilty that one cannot argue on the basis of concentration gradient that these substances are being produced in the fetal circulation, I should offer as additional evidence Dr. Jailer's observations on Addisonian females. These women prior to pregnancy were excreting essentially no 17-ketosteroids. During their pregnancy they began to excrete more and more. That is an ancillary piece of evidence favoring the fetal circulation as the producer of 17-ketosteroids during the latter part of pregnancy (*J. Clin. Invest.* **29**:1430, 1950).

Serum Corticoids in Liver Disease. Dr. R. Klein, Dr. C. Papadatos, J. Fortunato, M.S., Camilla Byers, B.S., and Dr. A. Puntereri, Pittsburgh.

In order to evaluate differences in blood corticoid responses to common stresses, the factors affecting the disappearance of corticoids from the blood, as well as those affecting their appearance, must be understood. This study was undertaken to consider the effect of liver disease upon the conjugation of serum corticoids.

Both free and conjugated serum 17,21-dihydroxy-20-ketosteroids were determined before and after the administration of cortisone and corticotropin (ACTH) and before and after surgical stress both in normal persons and in patients with various types of liver disease. In addition, random levels of free and conjugated corticoids were measured in this group of patients and compared with similar levels in normal children and adults. Cortisone was administered in doses of 60 mg. per square meter of body surface, by mouth. Corticotropin was given intravenously in doses of 10 mg. per square meter.

The levels of corticoids, both free and conjugated, are lower in patients with advanced liver disease than they are in normal persons. Patients with mild liver disease have levels of corticoids that fall within the normal range. After the ingestion of cortisone, the level of free corticoids in patients with liver disease rises to a higher level and descends more slowly than does the level in normal persons under the same circumstances. In contradistinction, the level of conjugated corticoids in these same persons with liver disease rises minimally, if at all.

After operation and corticotropin, the patient with liver disease demonstrates a normal rise in free serum corticoids but little or no rise in conjugated corticoids. Since the amount of stress cannot be calibrated, the levels of free corticoid reached cannot be compared to the levels reached in the normal patient undergoing surgery. After corticotropin, the rise in free corticoid in the patient with liver disease is similar to that seen in normal persons.

Prevous work from this laboratory has shown that conjugated corticoids rise more slowly after stress and corticotropin than do free corticoids and have a slower rate of disappearance. It seems likely that the free corticoids are conjugated in the liver and then excreted via the kidney. There is no evidence as yet that conjugated corticoids have any physiologic activity in the circulation.

DISCUSSION

Dr. Alfred M. Bongiovanni, Baltimore: I am of course delighted with Dr. Klein's results, since they are so much like ours, and it is nice to have two people coming up with pretty much the same answer.

As Dr. Gardner has pointed out, methodology in this field still requires a great deal of attention. I am biased in favor of enzymatic hydrolysis of corticoids, although it appears that acid hydrolysis has given Dr. Klein satisfactory results.

I am posing a problem to Dr. Klein and myself. We have both administered steroids by mouth, and of course they circulate through the liver rather quickly. The enteral route might then result in a greater proportion of conjugated compounds than would be the case via a parenteral route. The possible differences should be explored. For example, in adrenal hyperplasia Dr. Wilkins has noted that if patients are treated with oral cortisone, the daily dose is larger than the intramuscular, and it is best administered in divided doses through the day. This might well be due to the more rapid conjugation and, hence probably, inactivation of the compound.

DR. C. N. H. LONG, New Haven, Conn.: I am not directly engaged in the determination of these compounds in the blood. At times I thank heaven I am not.

But there are one or two points that come up, particularly with regard to the last paper. I should like to put the first in the form of a question. It has been, I think, fairly well established by the recent work of Gallagher and his colleagues that the rate of disappearance of this material from the blood when injected intravenously is extremely rapid. I believe that within a matter of two or three minutes the blood is almost completely cleared of it. During that period, a very sizable proportion of the injected steroids, 20 or 30%, has already accumulated in the liver, where presumably they would undergo conjugation.

This, of course, has some interesting implications with regard to the mechanism of secretion and the value of blood levels at any particular time as a measurement of the adrenal secretion.

It is also very odd, judging from the work of Sayers, that corticotropin also disappears from the blood with extreme rapidity. I believe the half-life is estimated at less than two minutes. The corticotropin reaches the adrenal. Immediately, there is a discharge of the steroids, which in turn, apparently, from the isotopic work and other work, also disappear very rapidly and accumulate very largely in the liver.

The paper we have just heard would indicate that there is a conjugation of these steroids in this organ, and I presume that their circulation would result in the discharge of a considerable proportion of the conjugate into the intestinal tract, where it would be hydrolyzed again to an active steroid.

I wonder if we are not beginning to see something of the means whereby an initial large discharge from the adrenal sustains the blood level through the cycle (*a*) initial conjugation, (*b*) the discharge of the material into the intestinal tract, and (*c*) again the release of free steroid into the blood.

This is an extremely interesting paper, even though I agree that the methodology here is extremely difficult and often very hard to interpret. The existence of the conjugated form of the hormone in the blood should alter our interpretation of the events that follow the initial secretion from the adrenal cortex.

DR. ROBERT KLEIN, Pittsburgh: It seems that each year I present a paper here, Dr. Bongiovanni gives me another year's work. I agree with his suggestion, which is excellent, and maybe we can get around to doing it.

In answer to Dr. Long, obviously, I cannot answer it. I think this is a very important point. We were actually sorry that we had not given some of this material intravenously, before Dr. Gallagher's paper, but even more so afterward.

I think that one point might be brought up, and that is that the rate of absorption of this material from the intestinal tract is fairly varied. We have done serial determinations, and I think probably Dr. Kelley has similar results, and instead of having the peak absorption apparently around an hour or two, at times the peak absorption may be much later. This further complicates the problem.

As to methodology, I confess that this is probably the worst possible method. Glucuronidase has advantages, although in our hands it hasn't worked as consistently. We are destroying probably as much hormone as we are releasing, but I think that the differences stand and indicate some of the extent of the problem.

The Distribution of Lead Between Red Cells and Plasma After Treatment with Edathamil Calcium-Disodium (Calcium Ethylenediamine-Tetraacetate), as Determined by a New Method. DR. SAMUEL P. BESSMAN (by invitation), Washington, D. C.

The lead contained in the blood plumbism is confined almost exclusively to the red cells. As a result of this phenomenon, the renal clearance of lead is very low. After a single dose of edathamil calcium-disodium (calcium ethylenediamine-tetraacetate [disodium salt]), the plasma lead increases to levels equalling or exceeding the red cell level, frequently without any rise in total blood lead. Data will be presented on five patients. This "solubilization" and redistribution of lead probably accounts for the rapid loss of lead from the body on treatment with the chelating agent.

The determination of lead, requiring 2 ml. or less of blood or 10 ml. or less of urine, by digestion and extraction with dithizone, is performed completely in a glass-stoppered micro-Kjeldahl digestion tube. This eliminates all transfers, preventing contamination and speeding up the procedure, so that a complete determination can be performed in duplicate in two hours. Recovery of lead in the presence of 2.5% edathamil calcium-disodium is quantitative. The simplified procedure can be adapted as a routine laboratory determination.

DISCUSSION

DR. J. B. SIDBURY JR., Wilmington, N. C.: That there is a reduction in the concentration of lead in the red cells and a rise of the level in the plasma has been shown; however, it is conceivable that tissue lead may have contributed to the rise in the plasma lead concentration. The rise in the blood lead concentration in children with lead poisoning under treatment with calcium EDTA suggests that the latter possibility may be a real one. It is of interest that in adults under the same circumstances the blood lead concentration falls. This observation suggests that in the two groups there exists a difference in the rate of metabolic turnover of lead, or, more general, a difference in the availability of the tissue stores of lead.

DR. MILTON RAPOPORT, Philadelphia: First, I should like to congratulate Dr. Bessman for a very neat method for determining blood lead.

What I should like to ask is a point of information. As I understand it, the chelating agent carries with it some toxicity. Some of the substances or techniques which we have been using prior to the advent of the chelating agents are nontoxic. What I should like to know is, how much more efficacious is the chelating agent than citrates, which are proposed by Kety?

DR. SAMUEL P. BESSMAN, Washington, D. C.: Dr. Sidbury is correct that we haven't proved that the lead shifts into the plasma of the red cells by these experiments. We assume that when lead leaves the cell it must have shifted to the plasma or must have gone through the plasma in order to be excreted. I may be corrected in this interpretation.

In answer to Dr. Rapoport's question about the toxicity as related to the efficacy of therapy, the citrate increases the excretion of lead in lead poisoning somewhere around twofold to threefold at most. EDTA causes an excretion somewhere up to 50 to 100 times the ordinary excretion of lead.

In terms of toxicity, we have not had any serious toxicity. I know that Dr. Hodes had a case that possibly had hemolytic anemia, and Belknap reported some bone marrow changes which, on reexamination, turned out to be not significant because the bone marrow was contaminated with blood.

In regard to the Wishinsky report, that there is a drop in the prothrombin level, we are interested in that particular phenomenon, because in our patients, we, too, found a drop, but we also found a rise with continued therapy. We believe that it might be due to the circulating EDTA effect in vitro on the prothrombin time, whatever we were measuring when we measured it.

"Microdrepanocytic Disease": Clinical and Laboratory Studies in a Large Negro Family. DR. M. E. LAHEY, DR. W. K. SCHUBERT, and DR. LUCIEN M. CORBEEL, Cincinnati.

The clinical and hematologic manifestations of a chronic hemolytic anemia resulting from the interaction of the genes for sickle-cell anemia and for Mediterranean anemia (microdrepanocytic disease) have been studied in a large Negro family. Six of 10 children were found to be affected with this variant of sickle-cell disease; the father and two children had the "minor" variety of Mediterranean anemia (microcythemia), while the mother and two children had sickle-cell trait (drepanocythemia). The report provides a basis for comparing this disease, previously unrecognized in the Negro, with classic sickle-cell anemia and with sickle-cell-hemoglobin C disease, the two common variants of sickle-cell disease.

Some of the patients had no complaints, while in others the symptoms were of moderate to marked severity. All exhibited hepatosplenomegaly, and all had a moderately severe anemia which was microcytic and hypochromic in type and which was accompanied by reticulocytosis, numerous target cells, normoblastic hyperplasia of the marrow, decreased osmotic fragility of the erythrocytes, and normal to slight hyperbilirubinemia.

Careful hematologic studies, with particular emphasis on the study of red cell morphology, aided in the differentiation of this disorder from other sickle-cell variants and were especially helpful when combined with similar studies of the parents. By means of paper electrophoresis, it was demonstrated that the pattern obtained in this disease was intermediate between that for sickle-cell anemia and the sickle-cell trait and thus allowed ready differentiation from the other variants.

DISCUSSION

DR. IRVING SCHULMAN, New York: I should like to ask Dr. Lahey whether determinations of fetal hemoglobin concentration were performed in this series of patients.

Also, it has always been disturbing to me a bit to have persons who are Negroes, let us say, or Chinese, or Burmese, or what have you, who have a chronic hypochromic microcytic anemia called Mediterranean anemia. I don't mean this from the point of view of semantics, but merely to point out that we do not have a specific diagnostic method. There is no abnormal hemoglobin that we can specifically implicate. All we have is a familial type of disorder with small pale red cells.

Now, whether these all are based on the same pathology or pathogenetic mechanism, I don't believe we have any way of saying at this point. I think possibly in future investigations we may find that these are not all the same disorder, but merely variants which have in common the inability to synthesize normal amounts of normal hemoglobin.

DR. ARLISS H. TUTTLE, Memphis: I should like to ask whether attempts have been made in this series of cases to apply paper electrophoresis quantitatively in order to determine what per cent of these patients' hemoglobin was sickle hemoglobin. In patients with sickle-cell trait, the level of sickle hemoglobin is usually considerably less than 50%. Dr. Karl Singer has reported one case in which only 5% of the total hemoglobin was of the "S" type. In patients in whom the sickle trait is present in combination with another abnormal hemoglobin, such as hemoglobin C, the sickle hemoglobin tends to be considerably higher and usually represents from 45 to 50% of the total hemoglobin, the remainder being the other abnormal hemoglobin.

I noticed on the electrophoretic record which was shown that the "nonsickle" component of the patient with microdrepanocytic disease did not seem to have exactly the same mobility as the normal hemoglobin. I wonder if that cannot mean that this subject actually has a relatively high per cent of fetal hemoglobin. We have been able to demonstrate a difference in the mobilities of fetal and adult hemoglobin when relatively pure samples of each are analyzed by paper electrophoresis. Mixtures of the two, however, cannot be satisfactorily separated by this technique.

DR. ROLAND B. SCOTT, Washington, D. C.: I think this paper is important because it calls attention to the presence of genes for thalassemia minor in the Negro. We do not know the true incidence of the heterozygous asymptomatic carrier state (so-called Mediterranean trait or thalassemia minor) in the population. Although the hematological characteristics of the trait or carrier state have been described by hematologists, there is unfortunately no singular identifying test comparable to the one for the sickling phenomenon.

It is possible that the incidence of the asymptomatic thalassemia trait is higher in non-Mediterranean races than is generally appreciated. From our clinic we have observed and reported the following cases in Negro subjects: (1) severe Mediterranean anemia (thalassemia major) in a 2½-year-old boy whose parents and five other blood relatives were carriers of the thalassemia minor trait; (2) a 15-year-old boy presenting clinical and hematological evidence of sickle-cell anemia, whose nonsickling mother exhibited clinical, hematological, and electrophoretic findings compatible with a diagnosis of thalassemia minor. The father, who was dead, presumably was a carrier of the sickling trait gene.

DR. EUGENE KAPLAN, New Orleans: I should like to add two very brief comments. Unfortunately, the situation is getting even more complicated. A little less than six weeks ago, we learned for the first time that there is another hemoglobin now called E, and of all things, E resembles very greatly, as far as we have been told about it, many of the aspects of thalassemia.

As Dr. Schulman says, I think we have to be very open-minded about this and realize that paper electrophoresis is not the answer certainly in diagnosing the new hemoglobin E, which can only be recognized, as far as I know, by its electrophoretic pattern.

As Dr. Scott says, thalassemia may occur in the Negro, and it has been seen in two instances which are now in combination with C, that is, thalassemia C disease in the Negro.

DR. C. HENRY KEMPE, San Francisco: I have a comment regarding children of Chinese parents with Mediterranean anemia. In Hong Kong, there are 10 or more such children in addition to a number described by Dr. Henry Silver at Yale University School of Medicine. It has been pointed out by the professor of medicine at Hong Kong that the grandparents of these children all come from a small province on the mainland of China which lies directly opposite the Portuguese colony of Machow. It is likely that the proximity to Portuguese inhabitants in this possession may have a bearing on the incidence of Mediterranean anemia in Chinese chlidren, according to Dr. Silver and the professor of medicine at the University of Hong Kong School of Medicine.

DR. M. E. LAHEY, Cincinnati: I think I have a few questions that remain unanswered, insofar as Dr. Scott ansewered one of Dr. Schulman's questions, and Dr. Kaplan pointed out that it might not be a satisfactory answer in view of the present confusion in this particular field.

In answer to Dr. Schulman's first question, we did not do fetal hemoglobins, except insofar as the father's hemoglobin was analyzed in the Tiselius apparatus, using a phosphate buffer at pH 7.8, and two peaks were identified as normal and fetal hemoglobins. Dr. Tuttle, I feel that it is somewhat difficult to quantitate amounts of sickle and normal hemoglobins by paper electrophoretic technique, but we do plan at the present time to reexamine these hemoglobins in order to quantitate more carefully sickle hemoglobin, so that we might correlate those findings with the variation of clinical severity in these patients.

I should completely agree with you that this tailing off of the pattern in the microdrepanocytic disease is partially contributed to by a large amount of fetal hemoglobin, but nonetheless, I am sure there is also some normal hemoglobin present.

I should agree completely with Dr. Scott's other comments about the presence of thalassemia minor, or something very very similar to thalassemia minor in Negro children, and in addition to the patients in this particular family, we have within just the past month found two Negro children with thalassemia minor who heretofore were considered to have iron-deficiency anemias because of the symptoms noted.

Galactosemia. DR. H. W. BAIN (by invitation), DR. A. SASS-KORTSAK, DR. D. BOWDEN (by invitation), DR. S. JACKSON (by invitation), DR. N. FORD WALKER (by invitation), and DR. A. L. CHUTE, Toronto, Canada.

Galactosemia, or galactose diabetes, is a congenital familial inborn error of metabolism characterized by an inability to metabolize lactose and galactose normally. The essential features of the resulting syndrome are severe malnutrition, hepatomegaly, and the presence of a reducing susbtance (galactose) and often albumin in the urine. Lamellar cataracts have been present in most of the reported cases, when carefully searched for with a slit lamp. Mental retardation may occur. Jaundice is being reported in an increasingly large proportion of the cases, and failure to report it in others may be due to the fact that it is confused with physiological icterus of the newborn. Various types of liver lesions have been recorded in autopsy cases.

The purpose of the present paper is to present eight additional cases, seven of which have been discovered during the past three years. It is suggested that the diagnosis is frequently missed because at the time of admission to hospital the infant is usually sufferng from diarrhea, vomiting, or severe malnutrition and is given only glucose drinks. Consequently, the initial urinalysis does not show the essential clue of reducing substance, which appears only when the baby is receiving milk feedings. Since the initial urinalysis is negative, it is usually not repeated when milk feedings are restarted.

In seven of the eight patients, jaundice was an important clinical feature. All except those with the diagnosis in the first two weeks of life were markedly malnourished. Three had cataracts, two of which cleared on a milk-free diet.

Detailed laboratory investigation has been carried out on seven of the eight patients. Almost all have had serial determinations of serum bilirubin, cephalin cholesterol flocculation, thymol turbidity, blood cholesterol, galactose tolerance tests, serum protein with albumin, globulin and

gamma globulin fractionation, and urine paper chromatography for reducing substance. Several have had determinations of glucose tolerance, alkaline phosphatase sulfobromophthalein (Bromsulphalein) excretion, urine amino acid chromatography, serum amino acid chromatography. Cephalin cholesterol flocculation tests were abnormal in most of the patients before therapy was instituted and became normal with institution of a milk-free diet. Serum albumin levels were initially low but soon rose to normal.

Two patients have died. The remaining six have been followed for six months to two years and still show marked impairment of galactose tolerance but otherwise normal liver function tests.

There was a marked familial incidence in three of the five families. Genetic studies have been carried out on all of the patients' families. Also, galactose tolerance tests were done on the parents and siblings and were essentially normal.

One patient had had a sibling die of "intrahepatic biliary cirrhosis" in our hospital in 1941. Review of the history confirmed that he too had died of galactosemia. Because of this, all autopsy cases of "cirrhosis" for a 15-year period were reviewed. Of the 46 cases examined, 16 were of unproved diagnosis. Of these, three had clinical, laboratory (reducing substance in urine), and pathological evidence compatible with galactosemia. Six other cases had clinical and pathological evidence compatible with galactosemia.

Theories as to the etiology of the liver damage are presented, as are the pathological findings in two cases.

DISCUSSION

DR. HUGH W. JOSEPHS, Baltimore: I should like to ask what type of anemia of that study was present in these children. Recently, we had in Baltimore a child who was sent up to us with a diagnosis of congenital hypoplastic anemia with the bone marrow findings.

When he got to us, we did not get a bone marrow study until after the child had been taken off milk and the improvement taken place. By the time we had the study made, the bone marrow was already showing signs of regeneration, so that we couldn't definitely confirm that diagnosis. But he had transfusions before he had come.

I should like to know what sort of anemia these children had, and I should like to know also what their ages were when they had it.

DR. ASHLEY B. WEECH, Cincinnati: This is just a brief question. I should like to ask Dr. Bain to say a little bit more about what he called a mild splenomegaly, whether it was the type of palpable spleen that might result from pushing down the spleen from the enlarged liver, or whether he thinks there is a true splenomegaly.

DR. RUTH GROSS, San Francisco: We recently had the opportunity to reevaluate a 10-year-old child who had been diagnosed by Dr. Melenkoff as an infant having galactosemia. As an infant, this child was desperately ill and fitted very well into the category which has just been described. The interesting thing is that he did have cataracts and that he had a very large liver. Liver function tests were done and were distinctly abnormal. The child was also severely jaundiced.

During the intervening years, 10 years, we found he was uncooperative, did not come to the clinic often, and also did not follow the advice of physicians, so that this child had not really been on a restricted diet. However, he himself did not like milk, was not a milk drinker, and only consumed milk products in ice cream and such things as that.

The thing that was interesting about this child after 10 years was that we had no evidence of abnormal liver function. The liver was not palpable. A battery of liver function tests was done, which were completely normal. There was no reducing substance in the urine.

However, when we did a galactose tolerance test on this child, it was distinctly abnormal. Also, this child had a high fasting blood level of galactose, which was interesting.

One further comment is that we used the technique of AV differences in doing the galactose tolerance test, and it is very interesting that in this child who did have galactosemia there was very little AV tolerance, whereas in a normal child there is a wide AV difference, very much like the diabetic child in the glucose tolerance test.

DR. WILLIAM COCHRANE, Cincinnati: I should like to ask Dr. Bain two questions:

First, with regard to the mental development of these children. The failure of proper mental development seems to be irreversible in these children and is an important complication. The

original case in the United States, described by Mason and Townsend, when reassessed at 18 years of age had an I. Q. of only 64. In the follow-up of these eight cases, has there been a high incidence of mental defectives?

The second question is related to causation and the importance of early diagnosis of this disease. Following Lockhart and Roboz's article on diagnosis of galactosemia at 4 days of age by paper chromatography, the question arises of whether this disease occurs in utero? Thus, by doing paper chromatography on amniotic fluid one could possibly make the diagnosis on a subsequent sibling at the time of birth.

DR. D. H. BOWDEN, Toronto, Canada: I think Dr. Bain's investigation is another small step forward in the process of sorting out the hepatic fibroses of the first year of life. The slides he has shown of the pathology of galactosemia are important because they illustrate that in the first few months of life the fatal cases show a different histological picture from that seen in liver biopsies of children of one year or more. The latter have shown a portal type of cirrhosis.

Bell has suggested that fatty degeneration of the liver is the cause of the fibrosis in galactosemia, but the only fat estimation he quotes in his paper was one of 6% (wet weight), a figure not unusual in the terminal phases of many diseases. Fatty change was certainly not a prominent feature of Dr. Bain's cases.

It has been suggested that a definitive diagnosis of galactosemia can be made from the histological picture alone.

I think that the histological findings in this condition are probably not specific and that a presumptive diagnosis only may be made from the microscopic examination (Bell, L. S.; Blair, W. C.; Lindsay, S., and Watson, S. J.: *Arch. Path.* **49**:393, 1950).

DR. KLEINBERG, St. Louis: I should like to ask Dr. Bain two questions. First, with reference to this mental deficiency, as to whether brain lesions were demonstrable on the two cases, and also, whether any clinical hypoglycemia was demonstrable during the galactose tolerance test.

DR. H. W. BAIN, Toronto, Canada: In answer to Dr. Josephs' question regarding the type of anemia, I am sorry to say that I do not recall whether we investigated this point. The hemoglobin on admission was almost always below 9 gm. (Addendum: anemia was present in five patients at the time of diagnosis. Bone marrow in three was normal. Coombs tests were negative in all, red cell fragility normal in those done [two]. White blood cell count and platelets were normal. The red cells showed some anisocytosis and hypochromasia.)

Dr. Weech asked whether the splenomegaly was real or due only to the spleen being pushed down. Although the spleen was never enlarged more than 2 fingers below the costal margin, it was a true splenomegaly and appeared to be related directly to the duration of disease. The patient who had had his disease for nine months before diagnosis had the greatest degree of hepatosplenomegaly.

Dr. Gross commented on a 10-year-old patient. I must say that, by and large, the liver function tests in our patients returned to normal very quickly after treatment was started. However, in the patient mentioned above, who had had the disease for nine months before treatment and who had the greatest degree of hepatomegaly, the liver function tests did not return to normal for about 22 months.

We too, noticed that our patients with galactosemia, even on milk-free diets, occasionally had silght fasting levels of galactose.

Dr. Cochrane asked about the mental development of galactosemia patients. I wonder if the question of mental retardation is not related to the duration of untreated disease, as well as to the severity of the condition, as I believe that there are all degrees of severity. In one family, the first sibling was undiagnosed until 4 months of age, and now, at 3 years of age, he appears to his parents to be a little retarded. His younger sibling was diagnosed at one week of age, and now, at one year of age, appears perfectly normal to the parents.

I cannot answer Dr. Cochrane's question as to the possibility of trouble developing in utero. Our earliest diagnosis was made at 5 days of age.

Dr. Kleinberg, regarding the autopsy studies, there were no demonstrable brain lesions in the two who died. Both were too young and too ill to assess clinically before death. We did not observe any clinical evidence of hypoglycemia during galactose tolerance tests.

Developmental Defects in the Chick Embryo Following Infection with Newcastle Disease Virus. Dr. Russell J. Blattner, Mrs. Alice Polk Williamson (by invitation), Dr. Lydia G. Simonsen (by invitation), Houston, Texas, and Dr. G. Gordon Robertson (by invitation), Memphis.

A consistently high yield of gross defects (seen on whole mounts of chick embryos, magnification 20 times) of lens, otocyst, and neural tube in chick embryos inoculated with Newcastle disease virus has been shown to depend upon the combination of three key factors, namely, the site of inoculation, the amount of virus inoculated, and the developmental stage of the embryo. Of three strains of Newcastle disease virus tested, all produced the same types of defects. Study of serial sections of embryos inoculated at developmental stages ranging from 36 to 84 hours revealed defects also in neural crests, visceral arches, amnion, olfactory pits, and apical caps of limb buds. The organs primarily affected are those proliferating and differentiating most actively at the time of inoculation, provided they are exposed to direct contact with the inoculated virus. The histopathological changes are similar in all affected organs. Preliminary studies to determine the mechanisms concerned in the production of the defects showed that the virus is capable of multiplying in embryos of the early stages used in these experiments. Inactivation of the infectivity of the virus by heating or ultraviolet radiation inactivated also the ability to produce defects. Further study is in progress.

X-Ray-Induced Embryonic Malformations in the Rat: An Application to the Human Malformation Problem. Dr. Robert Brent, Rochester, N. Y.

In order to study the lethal and malforming effects of x-ray on developing mammalian embryos, it has been necessary to irradiate both the mother and the embryos. The following experimental procedure, utilizing 246 pregnant rats, was devised to eliminate irradiation of the mother. At the time of irradiation, a midline incision is made in the abdominal wall of an anesthetized pregnant rat. The pregnant uterine horns are brought to the surface. The maternal rat and all but several fetuses are shielded from the radiation administered. Thus, not only do we eliminated any possible deleterious effects resulting from irradiating the maternal organisms, but we also have irradiated and control embryos in the same litter.

The pregnant animals were irradiated on the 7th, 8th, 9th, 10th, 11th, or 12th days of gestation. They were then killed on successive days after irradiation, and the fetuses were studied grossly and histologically. A summary of the various malformations produced by radiation on different days of gestation is presented, along with a graph which compares the chronological embryonic development of the human and the rat. From the experimental rat data and the graph presented, a theoretical estimate is made of the x-ray-sensitive periods of the different organ systems in the human.

The clinical and experimental applications of this study are as follows:

1. The irradiation of embryos in shielded mothers results qualitatively in the same type of anomalies seen when the mothers are also irradiated.

2. It is apparent that certain malformations occur only in embryos irradiated at one particular stage, while other malformations seem to be produced readily at many stages during early embryogenesis.

3. Practically every type of malformation recorded in the human species has been recorded in our series of rat embryos. Because of the large number of malformations recorded, the relative incidences of different malformations is statistically meaningful. Furthermore, the frequency of malformations in the 8- to 12-day rat-embryo groups followed very closely the incidences of spontaneous malformations in the human. This would lead us to believe that the periods of radiation sensitivity for particular malformations are the same for many teratogenic stimuli, and therefore the vast amount of data obtained from the field of radiation embryology might be applied to the general problem of human teratogenesis.

4. Utilizing the graph comparing human and rat development, we can relate the sensitivity periods of the rat to periods of human gestation. Our data demonstrate that the central nervous system maintains its sensitivity for a period in the rat which corresponds to at least the first trimester of human gestation. This would explain the high frequency of central nervous system malformations in general. Carrying this comparison further, it can be estimated that major

cardiac anomalies could be induced during the period from the end of the second week to the middle of the third week of human gestation. On the other hand, aortic arch anomalies and an interventricular septal defect could be produced from the end of the second to the fifth week of gestation. These rare malformations had correspondingly shorter periods during which they could be induced by irradiation.

DISCUSSION

DR. JOSEF WARKANY, Cincinnati: Both Dr. Blattner and Dr. Brent have pointed out the existence of sensitive periods in embryogenesis and emphasized their importance for teratogenesis. I agree with these statements and with the conclusions of Dr. Brent. But I am afraid of some conclusions which could be drawn from his conclusions. One must not think that one can ascertain the time in which malformations originate from morphological findings. The time of the injury plays an important role in the formation of an anomaly, but the nature of the injurious agent and its intensity are also important for the development of the anomaly. It is not possible, therefore, to give an example, to deduct from the symptoms of Mongolism the time of its origin. Dr. Brent has shown that the rat embryo is insensitive to x-rays up to the eighth or ninth day of gestation. But it has been found recently that one can produce malformations at the seventh and eighth days by other injurious agents. By changing the intensity of x-rays, one can show that the sensitive periods can be altered too. Thus we were able to produce cleft palate in rats on the 10th, 12th, 13th, 14th, and 15th days of gestation by variation of the dose of radiation. A morphological symptom, such as a cleft palate, does not indicate, therefore, the time of the origin of the malformation. And the same is true for other congenital defects which are often determined at various periods of embryogenesis.

DR. ALEX J. STEIGMAN, Louisville: There is some evidence that would suggest, as has been pointed out by Dr. Warkany, that virus exposure of presumably immune persons may nevertheless result in deformed offspring, particularly in the case of rubella, which, as far as we know, is not associated with persistent high levels of human antibody.

Furthermore, Dr. Blattner suggested that some of the histologic sections suggested to him direct viral effect upon the embryo. I am wondering if he has had an opportunity to repeat this observation in flocks successfully vaccinated against Newcastle disease.

I should like to ask him whether there is evidence that other teratogenic modalities, such as cortisone or x-ray, have their effect through liberating latent viruses.

DR. WILLIAM A. REILLY, San Francisco: I should like to hear some more comments about the dose of radiation. Dr. Warkany has already touched on this point, but I think Dr. Brent should make some comments, for not every woman who gets even a therapeutic amount of radiation to her pelvis gives rise to a deformed infant, as far as I know.

DR. DAVID T. KARZON, Buffalo: I should like to direct this question to Dr. Blattner. There is a well-known potent toxin associated with the Newcastle-influenza group of viruses. This toxin may be demonstrated by the intercerebral injection of large quantities of Newcastle virus into a mouse, a host to which the virus is not adapted. It does not multiply in this site, although death of the mouse occurs within 24 to 48 hours. The toxin is considered to be a neurotoxin.

The conditions of the experiment presented today would favor the action of toxin directly on the embryo. I wonder if Dr. Blattner has had an opportunity to distinguish between a toxic effect and the effects of viral multiplication.

The theory has this added attraction. It was stated that when the Newcastle virus is inoculated peripherally, it does grow in the embryo, just as well as if it were inoculated into the central nervous system. Yet, after peripheral inoculation, it does not produce neurological effects.

Reversing the purpose of this experiment for a moment, I wonder if Dr. Blattner has a mechanism whereby he has shown for the first time neurotoxicity of the Newcastle virus in the chick embryo?

DR. JOSEPH STOKES JR., Philadelphia: I was very much interested in these excellent presentations. It seems to me a field in which a great many more of us ought to do a great deal more work.

I was wondering where Dr. Blattner got his table that indicated the disease which might be responsible for anomalies; also, whether he has seen many infants whose mothers have been

immune to rubella but who have shown congenital defects. It has been our impression that even though their mothers have been immune, there have been some infants who have had anomalies, possibly as a result of infection.

In epidemic hepatitis, the same thing seems to be true, that infants may still develop the disease in the first six months or perhaps before birth, despite immunity in the mother. I was wondering whether Dr. Blattner would discuss that subject.

I should also like to ask about irradiation, as to whether there have been any data covering the descendants of the pioneer radiologists who received so much radiation. Since there may be accumulative effect on the genes with succeeding generations who are irradiated, the findings in such grandchildren or great-grandchildren may be of increasing importance.

DR. RUSSELL J. BLATTNER, Houston, Texas: I think Dr. Warkany's comments concerning x-ray studies apply equally to virus. We have been impressed by the relationship between size of virus inoculum used and the kind of developmental defect observed. Final evaluation, however, must await further work along this line.

I do think the intensity of cellular injury must be of importance, as well as the vulnerability of the tissue undergoing rapid growth and differentiation. Such tissues seem to be more susceptible at these times.

Dr. Steigman, the eggs we use come from vaccinated flocks maintained at the A. & M. College of Texas Experimental Poultry Station. The titer of antibody present in these eggs would be uncertain.

The cortisone effect is a very interesting and important one. I have been much impressed with the work of Gregory Shwartzman, who, as you know, showed that cortisone does facilitate the invasiveness of viral agents. In conversation with him some years ago, he stated that one of the factors which led him to consider cortisone as being a facilitative agent was the clinical observation that pregnant women, who have a high level of cortisone in the blood, seem to be more vulnerable to virus infections, the most dramatic example being that of poliomyelitis.

Actually, there might be a significant relationship between the cortisone level in pregnant women and the injury produced in the embryo by the viral agent.

The only objective evidence of which I am aware that rubella infection can occur in a human subject without the characteristic skin rash was reported by Krugman and Ward. They demonstrated that under experimental conditions rubella infection can occur in a patient who does not have typical clinical manifestations of the disease.

I don't know of any reliable method for demonstrating rubella antibody in an experimental animal.

Dr. Karzon's comments are quite pertinent. We have been impressed with the fact that large amounts of virus must be used to produce these defects with regularity. We have inactivated the material with heat so that the inoculum is no longer infective. Material so treated does not produce the defects in the embryo. As to the toxin referred to in your discussion, I am interested to learn whether the toxin is heat labile. If it is a heat-labile toxin, then our experiments in which the virus was inactivated by heat would not differentiate the two effects, i. e., virus from toxin.

However, the material rendered noninfective did not produce the abnormalities in the chick embryo.

We also altered the infectivity of the inoculum by means of ultraviolet irradiation. We could not produce teratogenic effects with such inocula, which gives, I think, some indication that the toxin also is destroyed by ultraviolet radiation.

While we cannot be dogmatic as to conclusions in this matter, I am of the impression that the teratogenic effects are due to viral infection in the embryo. We have evidence of increasing titer of virus in the blastoderm. These are preliminary studies; however, there is evidence of cytodegenerative lesions which have some of the features of viral effect, and we have observed on microscopic study "bodies" which resemble inclusion bodies. Recently, a paper appeared describing "inclusion bodies" associated with Newcastle disease virus infection.

Dr. Stokes, these charts are from the literature. I shall supply you with the references.

I think that immunity in the parent is of considerable interest. Dr. Bela Schick has stated during the last few years than an apparently immune mother can transmit a viral agent to her

offspring. In the case of smallpox, we know that persons once immune gradually lose immunity through the years. It is quite conceivable that viremia in the mother might be present, producing injury in a vulnerable fetus, even where there were no recognizable clinical manifestations in the mother.

Verification is needed; however, it would seem entirely possible that viremia could occur in the pregnant woman, even in the absence of clinical disease.

DR. ROBERT L. BRENT, Rochester, N. Y.: Dr. Warkany brings up an important point concerning the interpretation of data obtained in the field of experimental teratology. First of all, two teratological agents producing the same anomaly need not act at the same time during gestation, and, for that matter, their mechanism of action need not be at all similar. Those in this field who think they can relate certain periods of gestation as sensitive periods for the production of certain malformations, by all teratogenic stimuli, are not on firm ground. It so happens that x-ray administration can be temporarily limited to such a short period of gestation that the sensitive periods can be determined better than with any other agent; but still there is a wide range of sensitivity for the production of many malformations. Thus, x-ray experiments can tell us a great deal about the range of the critical periods of organogenesis but cannot tell us the mechanism of production of identical malformations that have occurred spontaneously. Therefore, an individual anomaly or teratological syndrome cannot be thought of as having been induced at a specific time during gestation, because of the wide range of susceptability of most malformations. It is known that some malformations have very short periods of susceptibility, but these are the exceptions.

The second question asked by Dr. Reilly concerned the dosages necessary to produce changes in the embryos. In the rat, as little as 12.5 r reduced the size of the embryos irradiated on the eighth day of gestation. On the ninth day, 50 r is able to produce malformations. As is well known, the older the embryo at the time of irradiation, the larger is the dose necessary to alter the development of that embryo. On the 8th day, the $L.D._{\infty}$ was approximately 130 r; on the 10th day, the $L.D._{\infty}$ was 200 r.

Dr. Stokes's question concerns itself with another field of radiation biology, namely, the genetic effects of irradiation. Gonadal irradiation with as little as 10 r per day results in a significant increase in observable mutations in offspring of these irradiated mammals. Since today we are interested in only the direct effect of irradiation on the developing fetus, we shall not concern ourselves with hereditable alterations of the gonads. It may be postulated that somatic mutations which may be produced in the fetus would be more detrimental to the organism because of the multiplication of these mutations as the fetus grows in the uterus and in childhood.

A Method for the Quantification of Case History Material in Pediatric Research. DR. JULIUS B. RICHMOND and DR. ANN M. GARNER (by invitation), Syracuse, N. Y.

The evaluation of many childhood disorders depends upon valid and reliable life history information. Not only physiological alteration and the development and recurrence of symptoms, but also patterns of family interaction and environmental change receive attention in any complete study. Indeed, current pediatric practice focuses upon the social and psychological factors which may determine the occurrence of disorder and color its consequences to the patient and his family.

Interview and questionnaire techniques for obtaining relevant life history material have reached a fairly acceptable level of development. There are few methods, however, for treating the data quantitatively for research purposes. The present paper describes one approach to the quantification of case history information.

The method is a variant of Stephenson's Q-technique—itself a derivative of simple correlational procedures—in which judges sort items constructed to describe historical events, the sorting to be done on the basis of a prearranged symmetrical distribution. The method requires (1) the preparation of a detailed case history; (2) the development of hypotheses regarding the life history; (3) the construction of descriptive items relevant to the hypotheses; (4) the arrangement of these items by judges in a normalized frequency distribution; and (5) the calculation of mean scale positions of the items, of judge intercorrelations, and of item intercorrelations. The application of this method yields measures of interjudge agreement, item descriptions of what is "most

characteristic" of this history, and (if desired) statements of the unique trait structure of an individual patient. Comparisons among several patients whose histories have been so treated are also possible.

For illustrative purposes, the method has been applied to the life histories of two 9-year-old boys, one suffering from ulcerative colitis and one from phobic disorder. The hypothesis tested was that the constellation of maternal and infant traits in the early months of life is different for a psychosomatic child by contrast with a neurotic child. Consequently, the items constructed described many phases of infant development and behavior and parental attitudes and reactions toward these phases. Four judges and the patients' mothers sorted the items into eight categories on the basis of how characteristic of the child each item was. Intercorrelations indicated satisfactory reliability of the judges' ratings (average r 0.531 and 0.618) and differential disagreement among mothers and judges, in line with the hypothesis. Extreme items provided different pictures of the early lives of these two patients.

The Q-sort method makes possible the detailed numerical handling of data which in the past have been treated largely in gross and qualitative form. Any hypothesis and any items can be employed; consequently, the method could be fruitful in studying physicochemical states, as well as sociopsychological ones. On the basis of our preliminary results, we feel the method deserves further tryout and evaluation in many areas of pediatric study.

DISCUSSION

DR. PAUL HARPER, Baltimore: I should like to ask Dr. Richmond two questions. First, how much time does technique require, and second, how is the problem of interviewer bias controlled?

DR. HERBERT C. MILLER JR., Kansas City, Kan.: One of the things that comes to mind is the reliability of evidence collected by the historical method as compared with data obtained by direct observations. Examples of such comparisons are to be found in the literature. One that occurs to me has to do with the weight of babies at birth, a topic that has notoriously been viewed with skepticism unless substantiated by observed measurements. Yet, in the case of babies of prediabetic mothers—a group that is characterized by increased birth weights in a high percentage of cases—data on birth weight obtained by the historical method by Jackson (*Brit. M. J.* **2**:690, 1952) and by Kriss and Futcher (*J. Clin. Endocrinol.* **8**:380, 1948) have compared very favorably with direct observations made by others. More recently, Jackson has found by means of the historical method a similar trend toward increased birth weights among infants of prediabetic fathers in Cape Town and also in Boston (*J. Clin. Endocrinol.* **14**:177, 1954). The last-mentioned observations need to be confirmed by directly observed measurements. But it does seem as though the historical method can be of value, and Dr. Richmond's thoughtful approach deserves encouragement.

DR. ALFRED H. WASHBURN, Denver: I should just like to say a word, in the first place, to express my pleasure that somebody has really started trying to quantitate historical material, which I suppose most of us look at as having a large subjective bias.

It seems to me that this is a tremendously important thing to do. No matter how well some of us may do with the longitudinal approach to answering some of these questions, we are still going to be faced with the problem that the average person in practice is going to have to depend, in a great many instances, on historically obtained material. Unless people like Dr. Richmond try to work out some quantitative approach to the analysis of the significance of historical material, we shall never know how to apply the material we get from longitudinal studies.

One more word, if I may be permitted to say something in response to a discusser. While I am sure that some historical material does check nicely with observed data, let me just express a word of caution. We have found some of our mothers, when the child is around 10 years old, extremely inaccurate in giving us a history of what they think happened at 1, 2, or 3 years. We have in our records what did happen at 1, 2, or 3 years of age. Dr. Richmond himself brought out the difference between the two mothers in the trustworthiness of historical material.

DR. JULIUS B. RICHMOND, Syracuse, N. Y.: Dealing with some of the points which Dr. Harper brought out, the sorting technique for each judge and the kind of sorting we were

involved in usually takes a minimum of an hour, reading and digesting the narrative account and going through the sort, initially perhaps double that time, so that this is not a simple procedure and not something that can be done very readily.

The construction of the trait universes with which one deals, regardless of what hypothesis one is pursuing and regardless of what material one is dealing with, is a considerably more laborious task than is statistical evaluation. The interviewer bias which Dr. Harper brings up is an important point. It is related or has some implications also in the question which Dr. Miller has raised.

We were dealing and were interested in dealing essentially with the material which is obtained in the usual pediatric setting, I should emphasize, in which one does not hardly go into the deeper psychological problems which are involved in the material, and yet this historical material can be of great value, so far as the research is concerned.

I don't think we need worry about the interviewer bias as long as we can control, to some extent, the observations which the interviewer or interviewers are engaged in. In other words, one, I think, has to build into this system some type of control.

Dr. Miller has raised a very interesting point on how reliable historical material is as contrasted with direct observations. We qualified our presentation with the statement that in the long run we believe that the longitudinal observations, such as Dr. Washburn and many others are in the process of doing, I think will have much more reliability. But Dr. Washburn has indicated we cannot necessarily wait that many years, nor is it absolutely essential that we wait.

I should like to reemphasize in relation to this question that we built into our hypothetical construction the fact that the mothers might not be reliable; as a matter of fact, you may recall that in the mother of the psychosomatic child, her thoughts about the first year of life and her relationships to her baby during that year did not correspond very well with the judge's, and I think this is quite an important point. This was taken into the hypothetical construction.

This means that our next job must be to get at why these mothers either don't remember as well as the mothers of control children, the mother of the neurotic child, as in this study; why, if they are repressing something so severely, they cannot bring this out; or else the fact in the hypothesis is really so, and that is that during the first year of life these mothers were sufficiently remote from the actual care of the baby, that they have relatively little basis for remembering.

Urinary Amino Acid Excretion by Premature Infants. PATRICIA M. NORTON (by invitation), DR. EDWARD L. PRATT, and EILEEN HASSELMEYER, New York.

The urinary amino acid excretion has been studied in 11 healthy premature infants in the period from birth to 37 days of age. The birth weights of these infants ranged from 1,320 to 2,350 gm. Determinations of total nitrogen, alpha amino nitrogen (by the CO_2-ninhydrin method), tyrosyl derivatives, creatinine, and qualitative tests for cystine and reducing substances were made on 55 twenty-four-hour urine collections; 29 collections during the first week, 13 during the second week, and 13 during the period 15 to 37 days of age. Semiquantitative estimations of the free amino acids excreted in each sample were made by the two-dimensional paper chromatographic technique of Dent.

During the first 10 days of life, the averages for urinary creatinine and alpha amino nitrogen rose irregularly from low levels to a peak of 15 and 14 mg. per kilogram per day, respectively, with the creatinine rising at a slightly faster rate than the alpha amino nitrogen.

During the second 10-day period, there was a gradual and parallel fall in the average values for these two constituents to the levels of 13 and 12.5 mg. per kilogram per day, respectively, and thereafter they remained at these levels. The urinary amino nitrogen fluctuated around 4% of the total urinary nitrogen during the first 4 days, gradually declined to about 2.8% at 14 days, and slowly rose to slightly more than 3% at 30 days of age.

The urinary amino acid patterns as determined by paper chromatography for the prematures were compared with the patterns prepared by the same technique for adults plus children and also for infants 2 to 16 weeks old. The urinary amino acid patterns of the prematures are distinctive in four respects:

1. Taurine is present in large quantities during the first few days and then disappears.

2. Both proline and hydroxyproline are detectable in large quantities throughout the study. This is a unique finding.

3. Threonine and "lysine" (possibly a combination of lysine, hydroxylysine, and ornithine) are present in larger amounts than in the urines of infants, children, and adults.

4. The excretion of tyrosine rises to a high level around the eighth day and then declines following the beginning of daily vitamin C administration on the seventh day of life. Serine, glutamic acid, alanine, and aminoacetic acid are excreted on the first day at or somewhat above the usual levels for infants, rise during the first week, and gradually decline toward the usual infant levels. During the first month of life the excretion of histidine gradually rises to levels above that for infants but less than that for adults.

The qualitative cyanide-nitroprusside test was consistently positive for cystine during the first week. The strongest reactions occurred during the first few days of life and consistently decreased.

Throughout the study practically every urine specimen produced a "green with yellow precipitate" reaction with Benedict's solution.

DISCUSSION

DR. FABIO SERENI, New York: We have measured clearances of total *d*-amino-nitrogen and individual amino acids in premature children, older children, and adults.

Total alpha amino nitrogen in blood and urine were measured by the Van Slyke ninhydrin gasometric method. Individual amino acids were estimated by two-dimensional paper chromatography on electrolytically desalted samples of plasma and urine. The importance of desalting in obtaining a good resolution of amino acids in plasma and urine with the paper chromatography was pointed out by Consden and many others.

The clearance of total amino acids appears, on the basis of surface area, to be highest in premature infants between 1 and 2 months of age; lower values are seen in young premature infants; however, the later values are still higher than those we have seen in adults.

When the values are referred to the glomerular filtration rate, it appears that in all three groups of subjects, approximately the same fraction of filtered amino acid is reabsorbed. Individual amino acids can be divided roughly in three different groups on the basis of their clearances per 1.73 sq. m. of body surface.

The following amino acids have clearances higher than 2 ml. per minute: cistine, histidine, lysine-arginine, serine, glycine, threonine.

The following amino acids have clearances below 1 ml. per minute: valine, leucine-isoleucine, phenylalanine, tryptophan.

The following amino acids have an intermediate behavior: alanine, tyrosine, glutamine.

Glutamic acid and aspartic acid show very variable clearances.

DR. EDWARD L. PRATT, New York: We have not done any clearance techniques, so that I have no real comments to make, except that obviously in this general sort of low-power view of the situation, one sees that the renal clearances may play some role in defining this rather individual pattern that these babies have.

I don't have a lot of data on protein intake, and, as a mattter of fact, I have a sneaking suspicion that maybe this supposedly complex situation of amino-aciduria in the premature beyond the first few days of life may be just due to the fact that he is equivalent to an adult taking 180 to 200 gm. of protein a day. But it may not be as simple as that.

We have a little data on a few prematures slightly older, who were on a feeding which provided 16% of the calories as protein instead of 20%, and, actually, by these admittedly crude techniques, there isn't a lot of difference, so that perhaps my hunch and Dr. Kagan's are not going to work out.

Serum Deoxyribonuclease (DNase) Activity in Premature and Term Infants. DR. WILLIAM OBRINSKY, DR. NATHANIEL B. KURNICK (by invitation), and DR. ELAINE G. FICHTER (by invitation), New Orleans.

While the concept of neonatal hepatic immaturity is well established, data bearing upon functional differences between premature and term infants are meager. This communication reports the results of assays of the sera of premature infants and normal newborns for deoxyribonuclease (DNase) activity. Experimental studies in the rat reveal that portal vein plasma has greater DNase activity than does hepatic vein plasma, indicating that a substantial fraction of the

enzyme is removed from the circulation by the liver. In this animal, hepatic damage induced by anoxia or carbon tetrachloride causes a marked impairment in the ability of the liver to remove DNase. Human subjects with infectious hepatitis show high serum DNase activity; the livers of these patients thus also appear to be unable to remove the enzyme from the blood efficiently. An investigation of serum DNase activity in prematures and normal newborns consequently offered an opportunity for further study of neonatal hepatic function.

Thirteen paired maternal and cord sera, taken at delivery, were assayed for enzymatic activity. Except for two highly active cord sera, all DNase activities fell within the normal adult range. All cord sera showed greater activity than the corresponding maternal sera. The mean cord DNase activity of 55×10^{-4} units per millimeter did not differ significantly from the previously established normal adult mean of 51×10^{-4} units per milliliter. The mean maternal DNase activity of 16×10^{-4} units per milliliter was significantly lower than activities of cord and normal adult sera.

DNase activities were obtained at random in 36 term infants aged 1 day to 13 months and did not differ significantly from those of normal adults. The mean for the term infants was 59×10^{-4} units per milliliter. Seventy-three DNase determinations were performed on 34 prematures; of these, 60 were done serially in 21. High activities were found in many of the younger smaller prematures. The mean for prematures of 89×10^{-4} units per milliliter was significantly higher than that for term infants.

From these preliminary data it appears that prematures tend to have highly active sera early in life. Subsequently, DNase activity declines to normal, presumably as a function of increasing maturity. Analysis of the data does not reveal whether, for this function, maturation is better related to age or to weight. The experimental work in the rat and the occurrence of markedly increased DNase activity in patients with infectious hepatitis lead to the provisional interpretation that the high serum DNase activity in prematures results from inability of the liver to remove the enzyme adequately.

Two conclusions can be drawn from the data: 1. Irrespective of the cause of greater DNase activity, prematures differ significantly from term infants, whereas term infants show no differences from normal adults. 2. Mothers at term show a striking reduction in serum DNase activity, and, as a group, their difference from normal adults is highly significant. The cause and significance of this latter finding are not presently known.

DISCUSSION

DR. HENRY L. BARNETT, New York: I have nothing really to contribute. I think these are interesting observations in an important area which needs investigation.

The Age Distribution of a Neutralizing Substance Against Canine Distemper Virus in a Human Population. DR. DAVID T. KARZON (by invitation), Buffalo.

A heat-stable substance which neutralizes the canine distemper virus was demonstrated in human serum by means of a neutralization test employing a strain of canine distemper virus adapted to chick embryos. The neutralizing substance was found in high titer in pooled gamma globulin of human origin but was absent in other plasma fractions. The distribution of this substance in relation to age in more than 250 randomly selected hospitalized patients was as follows: The neutralizing substance was usually present in cord blood and in amounts approximating the mother's titer. Both the number of positive sera and the serum titers decreased from birth to the age of 6 months. Between the ages of 6 months and 2 years, neutralizing substance was rarely found. It rapidly appeared in children between the ages of 2 and 7 years and was present in more than 90% of the adolescent and adult population. Evidence for and against the identification of this substance as a true acquired antibody will be presented. The curve of neutralization response in the population is proposed as evidence for the presence of a ubiquitous infection of children with the canine distemper virus or an antigenically related agent.

DISCUSSION

DR. ALFRED FLORMAN, Long Island, N. Y.: I think that Dr. Karzon is to be congratulated. This is a very pretty piece of work. I should like to raise two questions.

First, the lesions on the chorioallantoic membrane are rather unusual. Most of us who work with viruses that go on the allantoic membrane are not accustomed to seeing linear serpentine-like lesions. I should be interested in knowing whether or not an attempt has been made to reisolate the virus from these membranes.

Second, I wonder if Dr. Karzon has had an opportunity yet to follow antibody titers on individual infants. We notice that all of his babies had titers at birth. Has he been able to do serial studies after birth to get an antibody disappearance curve?

DR. JOHN M. ADAMS, Los Angeles: It is very interesting to me to listen to a paper which, in part confirms a study which I reported to this society a couple of years ago. I am very pleased that at least one pediatrician has become interested in this problem. As a matter of fact, I am sure that there are a few other laboratories now, judging by the correspondence I receive, that are following this problem in an investigative way.

We have been working with distemper, as you know, for several years and have developed the serum neutralization test. We have been using canine distemper, which is a common respiratory disease in dogs, as a model disease. It offers an enticing model for us to study, inasmuch as the adaptation of the agent from human sources has been extremely difficult.

We have adapted the egg strain of the virus to mice. We are working with the Hela cell in tissue cultures, which we hope will be a very useful tool for this adaptive problem.

I should like to ask about the neutralization titers, as I am just a little concerned about the specificity of antibody when employing a dilution of 1:5 only. I should like to point out that we have gone up to very high dilutions with human serum, as high as 1:640, and still have neutralization.

I think the most convincing thing about Dr. Karzon's studies is that the baby at 6 months of age and up to about 2 years is absolutely negative at a 1:5 dilution; which is not much of a dilution to be working in, to be sure, but negativity in that age period, I think, is very informative.

DR. HERBERT ALLAN WENNER, Merriam, Kan.: I missed the first part of this paper, but Dr. Karzon had informed me of some of his results earlier. My only comment is that the data appear to be fairly convincing in regard to the acquisition of natural antibodies against canine distemper virus.

The curves remind me very much of the curves obtained in several studies with the Lansing type of poliomyelitis virus. That doesn't necessarily indicate that the reactive component in serum is true antibody, but the heat stability of the reacting component suggests that it is. Perhaps Dr. Karzon will want to do some further studies, such as trypsinizing the serums, in an effort to remove nonspecific inhibitors.

DR. ALEX J. STEIGMAN, Louisville: Dr. Karzon has done a great service in developing so highly specific a test, with good evidence that this is true specific antibody. Perhaps the question one might raise about it, other than the ones he mentioned, is the result of 100% in the age group shown, since one seldom observes a 100% response even to active immunization.

In some ways Dr. Karzon has done us a delightful service by presenting us with a virus for which we must now find the disease, somewhat similar to the Coxsackie virus situation a few years ago!

DR. RUSSELL J. BLATTNER, Houston, Texas: I wonder if you have made sections of the chorioallantoic membrane, and also I should like to know whether you have inoculated susceptible animals and demonstrated increasing antibody titer by this method.

DR. HENNESSY, Ann Arbor, Mich.: I should like to state that in influenza, in working with the population groups with the FM1 antigen in the adult range, 12 years and over, you can demonstrate antibody being present in over 92% of the population.

If you take all the variety of influenza viruses, the adults have very close to 100%.

DR. DAVID T. KARZON, Buffalo: The linear nature of the lesion has intrigued me very much. Virologists agree that the chorioallantoic membrane lesions of the pox group and other viruses are always round in form. Perhaps the question can be solved by pathological studies which we are in the process of doing, although my imagination doesn't allow me to conceive of the mechanism of production of lesions which, in limiting dilutions, may traverse the entire length of the chorioallantoic membrane.

We have followed a few individual newborns, and their titers have dropped very nicely during the course of the first six months. Incidentally, tests of all persons were run as numbered unknown sera, so we would not be biased in reading the lesions.

We, too, were worried with using such a low dilution of serum (1:5). We have enough information to know that, had we used a 1:10, 1:40, or 1:80 serum dilution, we would have obtained similar but lower curves. Furthermore, when an individual serum is negative for antibody at a 1:5 dilution, it is almost always completely negative even in undiluted serum.

If one uses unheated serum, nonspecific neutralization does occur. We have not attempted to do enzymatic digestion of the antibody.

The problem posed by the finding of a 100% incidence of antibody in the population bothered us. Most antibody titers, for example, herpes simplex, Coxsackie, and poliomyelitis viruses, reach an incidence of 85 to 90% of positives in the adult population.

Workers studying the incidence of influenzal infection, as stated by Dr. Hennessy, do not seem to be concerned with the 100% presence of antibody. This is one reason for the suggestion that the distemper antibody response may represent a recurrent type of infection, possibly of the mucous membranes, which constantly supports the antibody level.

Vaccinia Immune Gamma Globulin: Present Status of Clinical Applications. Dr. C. Henry Kempe, San Francisco.

In the past year, experimentally produced vaccinia immune gamma globulin has been evaluated during a field study in southern India in the prevention of smallpox and in the treatment and prevention of severe and dangerous complications of smallpox vaccination. These included the inadvertently infected eczema child, generalized vaccinia, and progressive vaccinia (vaccinia necrosum).

In a serologic survey of 5,000 recently vaccinated army recruits, it became clear that the concentration of neutralizing antibodies increased in direct proportion to the severity of local skin response to vaccination. The optimal time for obtaining maximal antibody response was found to be four to eight weeks after such vaccination. Vaccinia immune gamma globulin differs from regular gamma globulin by the fact that the 300 blood donors all had experienced a successful smallpox vaccination four to eight weeks prior to their blood donation. One pint (473 ml.) of blood thus donated resulted in the production of 5 cc. of vaccinia immune gamma globulin.

In the laboratory, the material was shown to possess large amounts of neutralizing antibodies. Early clinical experience with vaccinia immune gamma globulin in the prevention and treatment of complications of smallpox vaccination is of promise. It has been life-saving specific therapy for the universally fatal case of progressive vaccinia. Its use in the prevention of smallpox in the known exposed family contact was tested in the last smallpox outbreak in southern India. Family room contacts of known smallpox cases were either only vaccinated or vaccinated and then given vaccinia immune gamma globulin. Contact family groups were treated identically within the group and were alternated from family to family in an unbiased fashion. A close daily check was made on all 133 patient contacts studied for a period of at least 25 days after the last known exposure to the disease.

In the final analysis, 76 smallpox contacts received vaccination alone, while 57 smallpox contacts received vaccination followed by vaccinia immune gamma globulin. Among the control group, there resulted nine cases of smallpox, while in the gamma globulin group there were two cases of smallpox. These two were nursing infants, heavily exposed by breast feeding on the infected mothers throughout their incubation period in the smallpox ward. Two other infants, similarly massively exposed and given gamma globulin in larger amounts, escaped the disease altogether.

Summary.—Vaccinia immune gamma globulin appears to find a place in the therapeutic armamentarium in the prevention and treatment of complications of smallpox vaccination and in the prevention of smallpox in the exposed family contact.

DISCUSSION

Dr. Herbert Allan Wenner, Merriam, Kan.: Dr. Kempe's study contains persons in two categories, namely, those who were vaccinated and those who not only were vaccinated but also received immune gamma globulin.

I am curious to know if Dr. Kempe (or the study group) had the courage just to try globulin alone in the familial contacts. Perhaps I don't quite understand the circumstances pertaining to the clinical trial.

DR. ANDREW J. RHODES, Toronto, Canada: I wonder if Dr. Kempe was able to carry out any antibody studies. I notice he mentioned that many of these patients had previous vaccinations. One would think they might already have as much antibody in the blood as they would be likely to have following gamma globulin. I wonder if he has any antibody tests to refute or confirm this suggestion.

DR. BELA SCHICK, New York: I should like to point out that after the introduction of vaccination in Austria, in 1901, very soon all newborn children were vaccinated with smallpox vaccine in order to be sure that they were not exposed very soon after discharge, because the children were discharged very quickly after birth.

Therefore, the giving of vaccines to newborn children was introduced. The interesting observation was that the vaccine reaction was very mild: no fever, very little local reaction, and relative immunity of the child. The child had some symptoms.

Lately, in America, we are coming out with the advantage of early vaccination in the newborn child.

The second interesting fact I discovered several years ago—I asked the speaker whether he had any similar observation. The old folklore warned that any mother who had smallpox in her life, or was vaccinated, should never take care of a smallpox patient, because she may be immune against smallpox, but the embryo is infected with smallpox and comes to birth with some mild form of smallpox, and the child has really gotten the infection.

I think it would be interesting to learn whether such observations were made in India. I collected from the literature over 40 cases. As I pointed out, therefore, in rubella, even if the mother is immune against rubella, she can transmit infection from outside to her fetus, so the child can get some malformation, which we know from the information.

DR. JOHN M. ADAMS, Los Angeles: I should like to commend Dr. Kempe and ask him if these patients die of the virus disease, per se, or secondary complications of the virus infection, and whether he observed primary virus pneumonia due to this virus.

DR. C. HENRY KEMPE, San Francisco: We were unable to get permission from the authorities to use vaccinia immune gamma globulin alone and had to settle for a controlled study of smallpox family contacts vaccinated after exposure or vaccinated after exposure and receiving vaccinia immune gamma globulin as well. Gamma globulin administered 12 to 24 hours after vaccination did not affect the vaccination take, although we are theoretically sure that it would prevent viremia.

In reply to Dr. Rhodes' question, I should say that the population at risk in these family contacts in this study was by no means 100%, since over 80% of the contacts had had previous vaccination. For that reason, we had to get some index of the relative susceptibility by comparing the incidence of vaccinations and the number of vaccination scars in both groups. Antibody studies on these patients were not done, but as you see, not all got smallpox, and we should not have expected them all to do so, since over two-thirds of them had been vaccinated previously. Therefore, many people got gamma globulin in this study who certainly did not need it.

As to Dr. Schick's comment, vaccination of the newborn infant does frequently result in only mild reactions or none, because of the modifying factors of antibodies given transplacentally. I did see a child in India born with smallpox. The mother had never been sick at all, either just preceding her pregnancy or at any time during her pregnancy. We know this does occur.

To answer Dr. Adams' question, we did see primary pneumonia due to the virus. I am certain that there were many instances due to Staphylococcus.

Metabolic Observations on the Effect of Vitamin D in Fanconi's Syndrome. DR. ROBERT A. SALASSA (by invitation), DR. MARSCHELLE H. POWER (by invitation), DR. JOHN A. ULRICH (by invitation), DR. ALVIN B. HAYLES (by invitation), and DR. ROGER L. J. KENNEDY, Rochester, Minn.

Two patients, a girl aged 11 and a boy aged 16 years, who presented the clinical picture and laboratory evidence consistent with renal tubular failure without glomerular failure (Fanconi's syndrome) were the subjects of metabolic investigation. The study consisted of estimation of the

balances of sodium, potassium, chloride, calcium, and phosphorus and measurement of amino acids, ammonia, and titratable acidity of the urine during periods of administration of sodium bicarbonate, ammonium chloride, and vitamin D. The results indicate that sodium bicarbonate decreased, while ammonium chloride increased, hyperchloremic acidosis. Neither of these substances altered the excretion of amino acids in the urine. Administration of vitamin D was followed by correction of the value for serum phosphorus and of hyperchloremic acidosis, decrease in renal clearance of phosphorus and glucose, and decrease in the excretion of amino acids in the urine. Clinical improvement followed administration of vitamin D.

DISCUSSION

DR. HAROLD E. HARRISON, Baltimore. I am quite interested in this paper, because this whole group of cases, I think, may eventually throw a good deal of light on the physiology of calcification, or certainly the regulation of calcium and phosphorus metabolism.

There are several points. First, these are somewhat older children than in the original reports, and, as you may have noticed, in recent years there have been a number of reports of so-called Fanconi syndrome in adults who have osteomalacia, along with glycosuria, amino-aciduria, and chronic acidosis.

Fanconi's reports suggested that the younger children with this disease did not respond well to vitamin D, and it may be that perhaps the lesion in older persons might be more responsive to treatment. It may be a less severe form of the enzymatic disturbance.

I don't quite agree with Dent's classification, but it does indicate that there is a wide spectrum of processes which seem to merge, one into another. On the one hand, there is a group of clear-cut patients who seem to fall into what is called hyperchloremic renal tubular acidosis, who do not have amino-aciduria or glycosuria, and who respond quite well to alkalinization and vitamin D. They are fairly easily treated, if they are picked up before the kidneys become calcified.

On the other hand, there are the cases of Fanconi syndrome in early infancy, with dwarfism and severe rickets. These may go on to severe renal insufficiency and die in early childhood.

In addition, there may be acquired cases of the Fanconi syndrome. Experimentally, we think we have some reason to believe that we can produce a similar picture. Clinically, we have seen what appeared to be a classic picture of the Fanconi syndrome in a child with lead poisoning, who had rickets, glycosuria, amino-aciduria, and phosphaturia with hypophosphatemia, and who eventually made a perfectly complete recovery on citrate therapy, without vitamin D. I was delighted to hear from Dr. Weech that he has seen a similar case, who was studied by Dr. Brodsky, at Cincinnati, some years ago.

There is one question that I should ask. Is there any familial story in either of these two children which might give us some clue as to whether they have a congenital defect or whether they might have an acquired or slowly progressive disturbance in contradistinction to the severe form of Fanconi syndrome seen on a congenital basis with a strong familial history?

DR. WILLIAM M. WALLACE, Cleveland: Could Dr. Hayles indicate how he controls his vitamin D doses?

DR. SAMUEL Z. LEVINE, New York: I think that the comments made by Dr. Harrison are very relevant, because if these two patients represent a congenital enzymatic deficiency as characterized by the congenital form of the Fanconi syndrome, it would be the first time, I think, that a vitamin was able to ameliorate the condition for prolonged periods.

I am thinking, by analogy, of the congenital metabolic aberrations, alcaptonuria, and phenylpyruvic oligophrenia, and the absence of effect of vitamin C on those two conditions in contrast to the acquired types of tyrosinuria which are relieved by the administration of vitamin C.

It is, therefore, conceivable that these two cases actually represent an acquired form rather than a congenital defect.

DR. CHARLES U. LOWE, Buffalo: I should like to ask Dr. Hayles two questions, if I may.

The first is this: Did he measure total organic acids in the urine, and if he did, does he have any figure of the per cent of the organic acids which were alpha amino acids?

My reason for asking this is because we have seen patients who have an organic aciduria and a syndrome not dissimilar from the Fanconi syndrome, but in whom the alpha

amino acids constitute only a small fraction of the organic acids as opposed to the patient that Mason and McCum described, in whom, if I remember correctly, 85% of the organic acids were alpha amino acids.

The second question is more of a challenge. I wonder if the authors would care to speculate on the mechanism involved in this response to vitamin D.

DR. JACK METCOFF, Boston: I think the authors are to be complimented on a very excellent balance study. It is always difficult in patients such as these to get such interesting data.

I wonder about several points which I perhaps missed. One was the question of the growth of these children; another, whether there was any evidence of pyelonephritis, and third, I wonder whether any estimates of discrete renal functions were made. We have been misled on the basis of a normal NPN, with or without a slight acidosis, into assuming lack of significant impairment in renal function; however, discrete renal functions indicated significant impairment.

Finally, I wonder if there was any variation in the excretion of solutes and glucose from time to time during the course of observation of this child. For example, were there periods when neither glucose nor amino acids were demonstrated?

DR. EDWARD L. PRATT, New York: I think it is very proper to emphasize the heterogeneity of the patients that make up this syndrome, because I think in evaluating treatment you have to know what is the matter with the patient when you start, and I know that I took care of a child in whom the past history was probably highly reliable, in that the mother was a nurse, and saw her in her first attack of acute glomerular nephritis. She had been healthy before that. Later, a year or so, she came in with the typical clinical findings of this syndrome that Lignac described in 1924.

But what I should like to ask is—and I think it would be important in a way—were rickets present when the vitamin D was given, and then could this observation on the effect of vitamin D on the amino-aciduria be repeated without the presence of rickets, because patients with rickets will have an amino-aciduria which is diminished when the rickets are healed?

DR. SAMUEL P. BESSMAN, Washington, D. C.: Two points I should like to make: First is the symptoms relating to the administration of ammonium chloride. I think it behooves us again to emphasize this particular poisoning of ammonium ions. We have made a study of the role of ammonia in hepatic coma and have come to the conclusion that this poisoning is a part of many disease syndromes.

The second thing is that we had a case of Fanconi's syndrome, and from the standpoint of the enzyme lesion we were interested in seeing what carbonic anhydrase inhibitor would do to this patient. It didn't do anything.

We gave the patient 20 mg. per kilogram of body weight of acetazoleamide (Diamox), but the patient showed no change in the sodium or potassium excretion, no change in the blood levels of bicarbonate, and no change in blood or urine. The patient had an initial serum bicarbonate concentration of 12 mEq. per liter.

DR. ALVIN B. HAYLES, Rochester, Minn.: We are aware of the fact that the original description of Fanconi's syndrome referred to congenital defects of the renal tubules. We have seen such infants, but metabolic studies on them were unsuccessful for one reason or another. It is true that patients presented in this study are older than most patients observed with Fanconi's syndrome. In both cases symptoms had been present for several years before we first saw the patients. Both patients were considerably dwarfed.

Since this study was undertaken we have treated another patient with congenital renal tubular defects of the Fanconi type with relatively large doses of vitamin D. Although this patient has been observed for only a relatively short time, considerable improvement has been noted.

In answer to Dr. Wallace's question about the regulation of vitamin D, we have given enough vitamin D to raise the serum phosphorus level to normal or near normal. In the patients presented, this was found to be 200,000 to 400,000 units daily. Hypercalcemia has been observed with the bigger doses of vitamin D but has not been a problem with the lower doses.

We are aware of the fact that the administration of vitamin D in large doses may result in toxicity, but the gravity of the situation presented by these patients seems enough to justify a trial with the preparation. Other measures usually recommended in the management of these patients have not been very helpful, at least in our experience.

It is certainly true that there are marked variations in the symptom complex presented by these patients. We do not mean to imply that the results of the studies on our patients would be applicable to all patients with Fanconi's syndrome.

In answer to Dr. Rhode's question about the measure of amino acids, I can only say that the chemist assures me that the content of alpha amino acid nitrogen in the urine exceeded 10% of the total nitrogen content of the urine in both patients.

The study of the effect of vitamin D in Fanconi's syndrome originated in the work of Zetterstrom and Ljunggren, when they demonstrated increased phosphatase activity with water-soluble vitamin D. Decreased phosphatase in the tubules had been suggested earlier by two groups of observers.

It is true that anatomic abnormalities have been described in the renal tubules in patients who have died of Fanconi's syndrome. We should expect that there would be some patients in whom vitamin D would have no effect.

In answer to the question about creatinine clearance, in both of the patients in this study endogenous creatinine clearance was normal at the start and throughout the time of the study.

In answer to the question about the glucose excretion in the urine, variation in the excretion of glucose was not noted before the start of the metabolic study. In one of the two patients there was a definite decrease in the excretion of glucose following the administration of vitamin D. In the other patient we did not start off with this in mind, so that we do not know the exact variation of glucose excretion during the study.

I should like to thank Dr. Bessman for his comments. They were very interesting.

The Influence of Vitamin D on the Parathyroid Secretory Response to Hypocalcemia.

Dr. John D. Crawford, Dr. Donald Gribetz (by invitation), and Dr. Peter L. Hurst (by invitation), Boston.

The hypothesis that vitamin D acts directly to suppress the parathyroid secretory response to hypocalcemia has been tested in studies conducted on groups of intact and parathyroidectomized young rats fed a calcium- and vitamin D-free diet with and without supplements of vitamin D.

	Group I	Group II	Group III
Animal status	Intact	Intact	Parathyroidectomy
Vit. D_3 (I. U./day)	0	10,000	10,000
Growth (gm./day)	2.5	5.1	2.8
Parathyroid size	Large	Normal	Absent
Tetany	±	+++	+++
Serum conc. values			
Calcium (mg./100 cc.)	4.9	8.5	4.6
Citrate (mg./100 cc.)	3.2	5.6	3.1
Inorg. phos. (mg./100 cc.)	10.0	10.0	18.8
Alk. pptase. (B. U.)	98	58	60

The development of early severe tetany in Group II and III animals is taken as indicative of lower concentrations of ionized calcium than in the Group I animals, which showed mild tetany of late onset. In all three groups, external calcium balances were similar, 18-day losses equalling about 7% of the starting total body calcium. The skeletons of the vitamin-deficient animals showed characteristic radiologic, histologic, and chemical changes of rickets; those of the vitamin-fed animals showed diffuse osteoporosis.

The results are interpreted to suggest that (*a*) vitamin D inhibits the development of rickets but can cause a special type of skeletal demineralization independent of parathyroid influence, (*b*) vitamin D diminishes but does not totally inhibit the parathyroid secretory response to hypocalcemia, and (*c*) serum citrate concentration undergoes marked elevation as a result of the combined action of vitamin D and parathyroid hormone. The clinical implications of these findings in disturbances of calcium metabolism observed in newborn babies and in patients with conditions such as steatorrhea, kidney disease, and vitamin D resistance will be discussed.

DISCUSSION

Dr. Harold E. Harrison, Baltimore: I certainly enjoyed Dr. Crawford's paper. I suppose it is quite characteristic that what people in the rest of the world call orthodox is called paradox in Boston, and vice versa.

I think there is no question of the interaction of vitamin D and parathyroid function, and I think there has been further evidence shown today.

I should like to ask Dr. Crawford if he has any direct evidence that vitamin D ever increases phosphate excretion by decreasing renal tubular reabsorption of phosphate. It is true that in the parathyroidectomized subject, or patient with hypoparathyroid tetany, large doses of vitamin D reduce the serum phosphorus level. Dr. Klein and I tried to study that problem and found somewhat to our amazement that large doses of vitamin D increased the glomerular filtration rate in the hypoparathyroid patient, as measured by creatinine clearance, and the increased excretion of phosphate was entirely on the basis of increased filtration rate; tubular reabsorption of phosphate in milligrams per minute was not decreased. The effect of parathyroid extract, on the other hand, when given intramuscularly, was to diminish renal tubular reabsorption phosphate without increasing the filtration rate.

I should be very much interested if Dr. Crawford has any direct evidence of the other type of effect, a stable filtration rate and reduced tubular reabsorption of phosphate.

The effects of vitamin D and parathyroid extract on serum citrate levels are certainly in keeping with everything that has gone before. I should question the possibility that these concentrations of citrate could chelate enough calcium to produce hypocalcemic tetany due to un-ionized calcium. The concentration of citrate was about 2.5 millimolar.

On the basis of the ionization constant of the calcium citrate complex it seems inconceivable that this concentration of citrate could lower the ionized calcium to tetany levels when the total serum calcium concentration was 8.5 mg. per 100 cc.

Since the animals obviously did have tetany, I think Dr. Crawford should search for some other explanation for the low concentration of ionized calcium.

Dr. Wallace W. McCrory, Philadelphia: I should like to ask Dr. Crawford if possibly I missed a point here. I don't quite see a clear demonstration that the vitamin D group provides a demonstration of a lack of responsiveness of the parathyroid gland to hypocalcemia. In the group in which the parathyroid gland failed to show increase in size, as I understood the data, there was no associated hypocalcemia. This, it would seem to me, is a hypothetical point rather than one demonstrated.

I should like information on another matter if possible. The author mentioned in the abstract that the balances on the animals were essentially similar. In view of the differences of serum calcium concentrations, I think one would expect a considerable urinary calcium loss at normal serum calcium levels and practically none at low levels.

I should be interested in whether or not larger amounts were lost in the urines of the animals with the normal serum calcium levels.

Dr. John D. Crawford, Boston: I thought Dr. Harrison would not ask his first question, since I interpreted his remarks in the presidential address to the effect that he had been able to demonstrate what we have called the "orthodox effect" of vitamin D.

The slide shows data obtained on parathyroidectomized rats given three different orders of dosage of vitamin D, and in Section A, urine phosphate excretion is plotted against glomerular filtrate phosphate. You can see that at any given level of glomerular filtrate phosphate the urinary phosphate increases in proportion to the dose of vitamin D. That is my best demonstration of the orthodox action of vitamin D.

As to the citrate concentration, Dr. Harrison, you are quite correct that the observed elevation of citrate is inadequate to account for a serum ionized calcium concentration lower in the tetanic than nontetanic animals. However, the fact that this tetany was specifically reversed by the administration of calcium in small amounts suggested to us that there was indeed a low level of ionized calcium in the serum of these animals. We shall have to look further for whatever agent it may be that chelates—using the word loosely—the additional moiety of calcium in the serum.

In response to Dr. McCrory's question, we are forced to admit that he, too, is quite right. If we consider only total calcium, we must conclude that there was insignificant hypocalcemia in the vitamin-D-treated animals. The tentative conclusion which we favor at the moment is as follows: These data suggest that vitamin D acts directly to diminish the parathyroid secretory response to low levels of ionized calcium.

The Use of Radioactive Iron in the Study of Erythropoiesis and Iron Metabolism.

DR. LEONARD APT, DR. MYRON POLLYCOVE (by invitation), and DR. JOSEPH F. ROSS (by invitation), Boston.

The pattern of iron metabolism was studied in a group of normal children and in patients with anemia.

Tracer doses of Fe^{59} bound to plasma protein were given intravenously. Simultaneous serial measurements of radioactivity were made in three body compartments over a period of 10 to 14 days: (1) circulating plasma iron, (2) hemoglobin iron, and (3) over representative areas of the liver, spleen, bone marrow, and nonspecific soft tissue, by means of a mobile scintillation detector. Employing gamma-ray counting techniques, the fraction of the total plasma iron removed each hour and the net incorporation of iron (in per cent) in the formation of circulating hemoglobin were determined. The movement of Fe^{59} within the human body was detected by external monitoring.

The patterns of iron kinetics were uniform in a group of normal children ranging in age from 2½ to 12 years. Between 35% and 70% of the total plasma iron was removed each hour. The same range was obtained in a group of normal male adults. The rate of plasma radioiron turnover was approximately the same as that found in the normal adults: 0.38 ± 0.06 mg. per hour per liter of blood volume. External body monitoring revealed that the bone marrow was the only significant site for the accumulation of the tracer iron. The rise in the marrow site counting rate paralleled the fall in the plasma. In 7 to 10 days, 90 to 100% of the tracer iron was incorporated into circulating erythrocytes. The decline in the marrow site counting rate occurred simultaneously with the appearance of radioiron in the circulating erythrocytes.

In a group of nonanemic children, whose hemoglobin and serum iron levels were in the lower range of normal, the fraction of the total plasma iron removed each hour was about twice that of the normal subjects. The accumulation and discharge of iron into circulating hemoglobin iron was one to two days earlier than in the normal subjects. This pattern was exaggerated in anemic persons in proportion to the decrease in hemoglobin and serum iron levels. This method of study made it possible to detect clearly mild iron-deficiency states in presumably normal children. The rate of plasma iron turnover in the "nonanemic" and anemic children was at the upper limits of normal.

The normal iron kinetic pattern (plasma → bone marrow → erythrocytes) was deranged in a series of patients with various hematologic disorders. In a patient with refractory anemia with erythroid aplasia, the movement of radioiron was from plasma to liver. There was no rise in the marrow site counting rate: no radioactivity appeared in the circulating erythrocytes. In a patient with congenital hemolytic jaundice there was a rapid removal of radioiron from the plasma by the bone marrow, followed by a rapid depletion of tracer iron from the bone marrow. Simultaneous with the decline in the marrow site counting rate and the appearance of labelled cells in the circulation, there was a threefold rise in the spleen site. This suggests a random destruction of erythrocytes by the spleen. The maximum of injected tracer iron incorporated into the circulating erythrocytes was 60%. After splenectomy, the iron kinetic pattern reverted to normal.

A patient with erythremic myelosis (di Guglielmo's disease) had the following abnormal iron kinetic pattern: radioiron moved from plasma to bone marrow to liver and spleen. Only 5% of the injected tracer appeared in the circulating erythrocytes.

The simultaneous correlation of the movement of Fe^{59} in the plasma, tissues, and erythrocytes provides a sensitive, dynamic, and functional approach to the study of the metabolism of iron and erythropoiesis in normal and pathologic states.

DISCUSSION

DR. GEORGE GUEST, Cincinnati: I should like to offer compliments on this excellent study, which marks an important advance in methods for quantitative demonstration of borderline iron deficiencies.

Many studies on nutritional anemia in infancy in the past have demonstrated that iron deficiency is likely to exist in infants in the second year even when the hemoglobin of the whole blood is within normal limits. In our survey studies done in Cincinnati some 20 years ago, when a large number of children were followed through more than five-year periods, we noted that

during the evolution of iron-deficiency anemia the red blood cells first decreased in size, then in hemoglobin concentration, before there was any significant change of hemoglobin in the whole blood, owing to compensatory increases in the red blood cell count. When the infants with slight microcytosis and hypochromia received iron as a dietary supplement, the mean red cell volume increased and the concentration of hemoglobin in packed cells increased, while the level of hemoglobin in whole blood did not change at all as the elevated red cell counts fell to normal.

The shift in labeled iron reported by Dr. Apt and his co-workers affords a much more sensitive means of measuring the avidity with which deficient cells can take up iron. It is an admirable advance in methodology.

DR. IRVING SCHULMAN, New York: I should like to add my compliments to those of Dr. Guest on this beautiful study. I am just sorry we didn't have a chance to study the slides more closely. One of the earlier ones I had an opportunity to watch was the one concerning the changes in the normal person, and this disturbed me a bit and seemed to effect some of my previous concepts about iron metabolism. This was a slide concerning what happens in a normal male.

A normal person should have several hundred milligrams of iron as iron stores in the liver, and we got the impression from the slide and the data shown that the administered radioiron went promptly to the marrow and promptly came out in the blood.

This would indicate that administered iron is used preferentially to that which is stored in the body, something which I don't think I personally believed before. This would have practical implications in evaluating the use and efficacy of iron in the treatment, let us say, of premature infants, and of the anemias which occur in the latter part of the first year, because it might indicate, as many people have suggested, that medicinal iron administered from the outside is better used than iron which the baby has in his own stores.

DR. CARL H. SMITH, New York: I wish to congratulate Dr. Apt on his excellent exposition, which clarifies the pathophysiology of iron metabolism in its various compartments. One of the important features in his presentation relates to the continuous shift in the internal metabolism of iron from place to place where hemoglobin is synthesized and red cells are produced. The level of serum iron reflects, therefore, a balance between iron absorbed, iron utilized for hemoglobin synthesis, iron released by red cell destruction, and the size of storage depots. At any particular time, the serum iron cencentration represents an equilibrium between iron entering and leaving the circulation, so that values for serum iron and latent iron-binding capacity fluctuate constantly, although specific patterns can be detected, just as Dr. Apt has demonstrated.

DR. LEONARD APT, Boston: I should like to make a few preliminary comments before coming to the question raised by Dr. Smith, which is, does the failure to detect a relative rise in radioactivity over a tissue site by the scintillation detector mean that no hemoglobin is being formed there? I presume he had particular reference to the initial part of the ferrokinetic study, when the plasma is being depleted of the tracer iron and the sacrum (as representative of the bone marrow) is the only site with a significant rise in the counting rate.

It is well to stress that the in vivo analysis of radioiron is not a strict quantitative determination. A rough quantitative statement, however, can be made in regard to the sensitivity of the external monitoring technique as applied to the results obtained in comparing one subject with another. With normal bone marrow function, which incorporates 90 to 100% of the circulating iron into hemoglobin, measurements are obtained with the scintillation counter which are at least 10 times greater than amounts which are easily detectable with the sensitivity of the instruments we presently employ. Therefore, we can say that if there is no detectable rise or fall in the counting rate over the bone marrow that the incorporation of iron into hemoglobin is less than 10%.

One could postulate that a rise in the counting rate may not occur if the uptake of radioiron, incorporation into hemoglobin, and release was extremely rapid relative to its removal from the plasma. However, this is very unlikely, because we have been able to detect the accumulation of radioactive iron over the sacrum even under the most extreme instances of erythroid hyperplasia, e. g., iron deficiency anemia, and hemolytic anemias. In these cases, the counting rates over the bone marrow remained high and stationary for at least 12 hours, even though the radioiron was removed from the plasma in less than 1 hour.

Dr. Schulman restated a concept about iron metabolism that was held for many years, namely, iron introduced into the circulation goes to the liver first and then to the bone marrow, where it is incorporated into hemoglobin. Our studies, and the data from other workers doing similar experiments, establish the metabolic pathway of tracer iron as plasma to bone marrow to erythrocytes. Only a minor accumulation (approximately 5%) occurs in the liver. The reason for the error in assuming that the iron went to the liver first was that nontracer compounds were used in the studies. Colloidal iron preparations were used by some workers. We have found by external monitoring measurements that labelled colloidal iron leaves the plasma rapidly and accumulates in the liver; it later goes to the bone marrow. Another source of error was that early preparations of radioiron were of low specific activity. The saturation of metal-binding globulin was often exceeded, and thus a considerable portion of iron was removed by the liver. In our studies, we use radioiron of high specific activity so that the saturation of metal-binding protein is kept within normal limits. The net effect therefore is not the introduction of new iron into the circulation but merely labelling of the circulating plasma iron already present.

It cannot be inferred from our studies that administered iron is used preferentially to that which is stored in the body. Our studies merely show that the circulating iron is removed almost exclusively by the bone marrow. The circulating iron is the result of the equilibrium between the removal of plasma iron by the bone marrow and the entrance of iron into the plasma from storage depots, intestinal tract, and other sites yet undetermined. To emphasize again, we have not administered iron or labelled any iron in the storage sites. Therefore, no conclusions regarding the comparative utilization from these sources can be made.

Neutralizing Antibody Responses Following Natural Infection with Poliomyelitis Viruses: Study with Prototype Viruses and the Patient's Own Virus. Dr. C. Arden Miller and Dr. Herbert A. Wenner, Merriam, Kan.

Previous efforts to detect and measure antibody responses following poliomyelitis infection were handicapped because there was no reliable way to detect antibodies against poliomyelitis viruses except in monkey protection tests. These tests are expensive and laborious. Interpretation of results obtained from earlier studies was difficult because the existence of three immunologically unrelated types of poliomyelitis viruses was not appreciated. Consequently, precise information concerning the antibody response to infection with poliomyelitis viruses in humans has been lacking. The recent development of tissue culture techniques has made the measurement of antibodies against all three prototype viruses a simple procedure. The present study was undertaken with the expectation that this newer technique would lead to a better understanding of the antibody response to this disease.

Plan of Study and Method.—During the summer of 1952, 14 children, aged 18 months to 14 years, with an early clinical diagnosis of poliomyelitis were selected for detailed serologic study. All of the children had pleocytosis in their spinal fluid; two of them had bulbar, six of them had spinal paralytic, and six of them had nonparalytic type of disease.

Serum specimens were obtained within a week after the appearance of the first symptom. Further specimens were obtained every week for 3 weeks, every two weeks for 1 month, every month for 4 months, and again 16 to 18 months after the acute illness. This schedule could not be rigidly followed for all patients.

Stool specimens were obtained from seven of the children during the acute illness. Type 1 poliomyelitis viruses were recovered from six of these specimens, and Type 2 from the seventh.

Neutralization tests were done in monkey kidney epithelium tissue cultures, using 32 times the 50% infectious dose of the three known prototype poliomyelitis viruses and the patient's own virus when available. Serum specimens were tested in serial fourfold dilutions. All the serums from a patient were tested on the same day against the same virus.

Results.—Thirteen of the 14 children had antibodies in all serum specimens in titers greater than 1:128 and as high as 1:8,192 against at least one prototype virus. I am calling this the major antibody response. In 10 cases, the major antibody response was Type 1, and in one patient it was Type 2. Two patients had major antibody responses against two viruses.

One of the 14 children did not have antibodies against any of the poliomyelitis viruses, though his clinical history was quite compatible with a nonparalytic infection. In the third month, this patient's Type 2 antibody titer rose, after six negative serums, to 1:5,120, possibly indicating an inapparent poliomyelitis infection several months after an erroneous diagnosis of poliomyelitis.

In the seven children from whom virus was recovered, neutralizing antibodies against the patient's own virus closely paralleled those against the homologous prototype virus. When differences in titer did occur, they were in favor of higher antibody titers against the patient's own virus.

The major antibody type and titer were presumed to be the result of the infection which began our study. The identity of type between the major antibody and the virus recovered from the patient's stool supports this belief. The problem is less simple for the two patients with two major antibodies. From one of these patients, having high titers against virus Types 1 and 2, Type 1 virus was recovered. From the other patient, with antibody Types 1 and 3, both in high titer, no specimen was available for virus isolation.

Ten of the 14 patients had antibodies against more than one prototype virus. Two of these have already been described as having major antibody levels against two prototype viruses. The other eight patients had one major antibody type and another one or two types present in low or minor titers.

The incidence of heterotypic antibodies increased with the age of the patient. All of the children over 8 years of age had more than one antibody type. Only half the children under 8 years of age had more than one antibody type.

Except in a few instances, the antibody titers were as high early in the course of the infection as later in convalescence; and the titers did not diminish during the 18 months the patients were studied.

There appeared to be no correlation between the clinical course of poliomyelitis and the antibody response.

Summary of Results and Conclusions.—As early as two days after the first apparent symptom due to poliomyelitis, specific antibody titers were fonud at peak levels. This indicates to us that overt symptoms are late occurrences in the pathogenesis of poliomyelitis.

Most patients convalescing from poliomyelitis had antibody against more than one prototype virus. This serologic overlap may be interpreted several ways:

(*a*) Some virus strains may have antigens common to two or three of the virus types, so that infection with one of these strains produces more than one type of antibody. There is no direct experimental evidence to support this hypothesis, though there is ample precedent for it in other microbial families.

(*b*) An alternative interpretation is that some patients may have had antibodies persisting from an old poliomyelitis infection caused by a different type of virus from the one which began our study. In favor of this interpretation of multiple heterotypic infection is the finding that the incidence of heterotypic antibodies increased with age and presumably with the opportunity for multiple infection to occur. Left unexplained by this interpretation are the very low titers of most of the heterotypic antibodies. The infections we studied, eight paralytic, five nonparalytic, and one inapparent, all caused exceedingly high titers which did not diminish in at least 18 months.

Finally, the neutralization test, as performed by us, appears to have limited value in positive diagnosis of such an acute illness as poliomyelitis. A rise in antibody can be demonstrated in only a few cases, and a high antibody titer may indicate an old infection as well as a current one.

DISCUSSION

DR. ROBERT WARD, New York: We have been doing somewhat similar studies to those that you have just heard, and I should like to cite some examples to illustrate two things.

First, rises in antibody from acute to convalescent phase were as much as one-hundred-fold. We have studied seven or eight patients' antibodies against their own virus, and in each case we have demonstrated antibody rise of at least fourfold.

The second thing concerns the contribution of the laboratory to the clarification of the diagnosis.

The first patient is a patient of Dr. Hodes, who gave the following story: Seven days before he came in to the Mount Sinai Hospital, he developed fever and sore throat. The physicians gave him penicillin, and he was well for the next three days.

Then fever and facial paralysis occurred, and soon after that, the patient had pooling of secretions in his pharynx. A diagnosis of poliomyelitis was made. His spinal fluid showed 40 mononuclear elements.

High fever was sustained for the next three to four days, then his temperature fell by crisis, and a pink maculopapular rash emerged. Dr. Hodes wondered whether possibly he could have a rare neurological complication of roseola infantum. He made available some material, and we were able to recover Type 1 poliomyelitis virus from the patient's stool and demonstrated a fourfold serum antibody rise from acute to convalescent stage.

The second patient was a 24-month-old girl with a 12-day-old story of intermittent fever, vomiting, and irritability. She refused to sit or walk. The local physician said that she was weak because of lack of food. There was some disagreement among the members of our staff as to what the child was suffering from. She did have a stiff neck and absent deep tendon reflexes for a few days. She had 10 cells in her spinal fluid and then went on to make a complete recovery in a week. We got Type 2 poliomyelitis virus from her stools and demonstrated a threefold to fourfold rise in antibodies from acute to convalescent phase.

The third patient had fever and vomiting and refused to sit and to walk for thee days. Her temperature was 102 F. She had ataxia. The electroencephalogram showed a diffuse cerebral dysfunction pattern. Our neurological consultant thought that she had a lesion in the midbrain of unknown etiology, perhaps infectious. She had eight cells in her spinal fluid. We isolated Type 3 poliomyelitis virus from this patient's stool, and she had a one-hundred-fold rise in antibody titer.

The fourth one was a patient at Babies' Hospital, who had a typical story of poliomyelitis with a "double hump." She had developed very severe quadriplegia, which persisted, and the child was finally discharged with considerable residual paralysis. This patient had 14 cells in the spinal fluid. The virus that we isolated from the stool was nontypable. It had the following characteristics: It produced typical cytopathic changes in tissue culture. It produced fulminating prostrating poliomyelitis in two cynomolgus monkeys and no change in suckling mice. The patient developed better than a twentyfold rise in antibodies against her own virus.

We don't know what to call this virus from the characterization of it as far as we have gone, but I might say that a few years ago, before the elegant tissue culture method of Dr. Enders, Dr. Robbins, and Dr. Weller was available, it certainly would have been called poliomyelitis virus.

I should like to emphasize that the studies of Miller and Wenner, the gathering of data pertaining to the natural history of poliomyelitis infection, although perhaps not so glamorous, represent just as important an approach as the direct attack on poliomyelitis by passive and active immunization.

DR. ANDREW J. RHODES, Toronto, Canada: I should like to congratulate the speaker on this very interesting study. As far as I know, it is one of the most complete that has come out so far in which tissue culture methods have been used.

I wonder if I might ask the speaker to comment on the results shown in the following table; this relates to the results of neutralization tests carried out on the acute and convalescent phase sera of three representative patients with clinical "nonparalytic poliomyelitis" excreting Coxsackie virus but not poliomyelitis virus.

Neutralization Tests for Coxsackie and Poliomyelitis Viruses

Patient No.	Serum	Coxsackie Antibody Titer	Poliomyelitic Antibody Titers		
			Type 1	Type 2	Type 3
1.....	Acute	0	0	2.0	0
	Conv.	3.47	0	2.8	0
2.....	Acute	1.89	0	1.0	2.8
	Conv.	3.05	0	1.0	3.2
3.....	Acute	2.05	Less than 1.3	Less than 1.3	Less than 1.3
	Conv.	2.68	Less than 1.3	Less than 1.3	Less than 1.3

Patients 1 and 3 showed a fairly well-marked rise in Coxsackie antibody in convalescence; Patient 3 had high levels in both sera, with a slight rise. Until recently, we had to stop at that particular point in our laboratory tests on cases of suspect Coxsackie aseptic meningitis. Recently, however, we have been able to go further in excluding the presence of poliomyelitis infection in these patients by means of the poliomyelitis neutralization test. I should like some help from our speaker, as I find the results rather difficult to interpret.

In one group of patients, represented by Patient 1, there was no Type 1 or 3 antibody, but there were high levels of Type 2. It is possible that these patients had actually a Type 2 poliomyelitis infection as well as Coxsackie and that we just did not isolate poliomyelitis virus from the stool?

In the second group, represented by Patient 2, there was no Type 1 and little Type 2 but high Type 3 antibody. Is it possible that this group of patients were infected both with Coxsackie and Type 3 polio viruses?

The third group, represented by Patient 3, is the only one in which we can be at all certain that the true diagnosis was Coxsackie aseptic meningitis and not poliomyelitis.

These results with representative patients just illustrate some of the difficulties in interpreting poliomyelitis serological tests, particularly in nonparalytic cases.

DR. FREDERICK C. ROBBINS, Cleveland: I am not functioning at a very high level, and I am afraid I don't have anything of great importance to add.

I think that Dr. Miller's work is very interesting, and it is a compilation of that kind of data that we need very badly; as Dr. Ward pointed out, individual patients vary tremendously in their behavior. We have been doing, in very preliminary stages, similar work, attempting to work up patients in considerable detail with numerous blood serums. We don't have enough data yet to say, although we, too, are finding that we get rises against heterologous as well as homologous agents, in some instances, although in some cases we have been able to show good antibody rises, as Dr. Ward mentioned.

I might add that we have had considerable difficulty in isolating from stools stored as long as a year a Type 2 in several instances, where serologically they must be Type 2, but after repeated attempts in culture, we have not been able to get the agent out.

I should like to add one other thing. In studying patients, we suddenly realized we had to be very careful, because many of the patients from whom we were obtaining frequent specimens over a long period of time were severe cases that stayed in the hospital a long period of time and were cases that we could keep track of.

We have had two and possibly three cases that were almost certainly cross infections within the hospital, and this, of course, could foul up our data no end.

DR. C. ARDEN MILLER, Merriam, Kan.: I am pleased to learn that Dr. Ward has succeeded in demonstrating antibody rises. Our conclusions from the data that we have was not that the antibody rises did not occur, but that very likely our serum specimens were not early enough, or that our techniques were not sensitive enough to demonstrate them.

I think that what our data do show, and the few cases that Dr. Rhodes presented likely corroborate this, that the antibody titers are exceedingly high regardless of how early the specimens are obtained, whether or not a subsequent antibody rise occurs.

The problem of how much of an increase one should look for, I think, comes up. Two of the four cases that Dr. Ward told us about showed a threefold to fourfold increase in antibody titer, and I should only say that in following serum specimens for over a period of 18 months, we found that a threefold to fourfold increase or decrease occurred rather frequently. I think that this indicates that we need to appraise this technique in greater detail to know at just what point you say a rise in titer is or is not significant.

Dr. Rhodes has presented me with a knotty problem, that is, what is the significance of the high antibodies against polio viruses in his patients, particularly those patients who showed an increase in titers against the Coxsackie viruses? I should only say that from our data we should expect that high titers against poliomyelitis viruses might have existed in patients for a period of many years, and I should be reluctant to put a great deal of diagnostic importance on the height of the titers alone, particularly when his patients had an increase in titer against Coxsackie viruses after the acute infection.

(To Be Concluded)

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

STUDIES OF IRON REQUIREMENTS IN INFANTS AND CHILDREN: 1. NORMAL VALUE FOR SERUM IRON, COPPER AND FREE ERYTHROCYTE PROTOPORPHYRIN. PHILLIP STURGEON, Pediatrics **13**:107 (Feb) 1954.

On an average, the newborn infant serum, compared with normal adult male serum, is hyperferremic (soluble iron, 193 mg. per 100 cc.), hypercupremic (soluble copper, 51 mg. per 100 cc.), and in it free erythrocyte protoporphyrin is increased about twofold (erythrocyte protoporphyrin, 55 mg. per 100 cc.). Total serum iron-binding capacity appears to be 50% or more saturated.

At 12 hours of age, marked hypoferremia (soluble iron, 46 mg. per 100 cc.) is present, and the total iron-binding capacity, as measured in this study, is 100% saturated. There is slight, if any, change in the serum copper or erythrocyte protoporphyrin during the first few hours or days of life.

From 2 weeks through 1 month of age, an essentially normal pattern is present except for the slightly elevated (twofold) protoporphyrin.

By 4 to 10 months of age, on an average, the normal infant has the pattern characteristic of infancy, namely, hypoferremia (soluble iron, 50 mg. per 100 cc.), hypercupremia (soluble copper, 146 mg. per 100 cc.), reduced saturation of the total serum iron-binding capacity (12%), and elevated free erythrocyte protoporphyrin (erythrocyte protoporphyrin, 70 mg. per 100 cc.).

Extreme ranges in values are found in different persons at most ages.

The suggested explanation for these findings is that, on an average, the normal infant, relative to the adult, is totally depleted of his iron reserve, and that his state of "physiologic anemia" constitutes an additional, but lesser, iron deficit.

FROM THE AUTHOR'S SUMMARY.

FSSENTIAL HYPOPROTEINEMIA WITH TETANY. H. SCHONENBERG, Ann. pædiat. **182**:355 (May) 1954.

Schonenberg reports on a case of hypoproteinemia which has been observed for over eight years. Besides severe quantitative and qualitative changes of the serum protein, there existed hypocalcemia and hypophosphatemia, which on several occasions caused attacks of tetany. The electrophoretic changes in the serum are reported in detail. The result of the parathormone and the Ellsworth-Howard tests as well as the phenotype make one think that besides the hypoproteinemia there might exist a central disturbance of the calcium-phosphorus metabolism, subordinate to the hypoproteinemia.

FROM THE AUTHOR'S SUMMARY.

CYSTINOSIS. E. FREUDENBERG, Med. Klin. **49**:169 (Jan. 29) 1954.

Attention is called to the deposition of tyrosine in addition to cystine in the bone marrow of a patient with cystinosis. A simple method is given for its demonstration. In a case of cystinosis, compounds with energy-rich phosphoric bonds, such as yeast, adenylic acid, and adenosinetriphosphate were administered on the basis of the considerations of the great importance of the energy-rich phosphate bonds in many metabolic reactions. Yeast adenylic acid was given in a daily dosage of 50 mg. for six weeks and 20 mg. daily of adenosinetriphosphate for about one month. Previous medication had not been successful. The result of the treatment was seen in the disappearance of glycosuria which only occurred occasionally in traces, in the better regulation of the water metabolism, in the cure of the vitamin-resistant rickets, in the diminution of the amino-aciduria, in the diminution of the excretion of neural sulfur with increase of an organic sulfate, and in a pronounced growth impulse.

AMBERG, Rochester, Minn.

Vitamins; Avitaminoses

THE VITAMIN B CONTENT OF MILK PRODUCTS. J. B. HASSINEN, G. T. DURBIN, and F. W. BERNHART, J. Nutrition **53**:249 (June 10) 1954.

Hassinen and co-workers concluded from their experiments that sterilized liquid-milk products were found to contain from 33 to 64% (0.10 to 0.35 mg. per liter) and dried-milk products 69 to 89% (0.24 to 0.52 mg. per liter) of the vitamin B_6 activity of the fresh milk used in their formulation. The heating process used in industry for sterilization of liquid-milk products causes a considerable decrease in the vitamin B_6 content. The decrease not only occurs during autoclaving but continues at a relatively rapid rate for as long as a week afterwards. Pyridoxine added to the sterilized liquid-milk products is more resistant to heat inactivation than pyridoxal, pyridoxamine, or the naturally occurring vitamin B_6 in milk.

FREDEEN, Kansas City, Mo.

CONGENITAL ANOMALIES IN THE RAT PRODUCED BY EXCESSIVE INTAKE OF VITAMIN A DURING PREGNANCY. SIDNEY Q. COHLAN, Pediatrics **13**:556 (June) 1954.

Excessive intake of vitamin A during pregnancy in the rat results in a marked litter failure. However, when litters are carried to term a variety of gross congenital anomalies are produced which include: exencephaly, eye malformations, cleft palate, shortening of the mandible and maxilla, spina bifida with meningocele, and hydrocephalus. Of 148 offspring of vitamin A-fed maternal rats, 77 exhibited gross malformations (an anomaly rate of 52%). There were no congenital anomalies observed in 1,201 control young.

The 7th to 10th day of gestation was found to be the period critically susceptible to the teratogenic effect of vitamin A excess.

The stage specificity of various environmental agents and the possible mechanism of action of the teratogenic effects of maternal vitamin A excess are discussed.

FROM THE AUTHOR'S SUMMARY.

THE PO_4 METABOLISM IN VITAMIN-D-RESISTANT RICKETS. W. RUPP and W. SWOBODA, Helvet. paediat. acta **9**:249 (July) 1954.

It was demonstrated in six personal cases that the variety of vitamin-D-resistant rickets named by Fanconi *phosphat-diabetes* is due to a deficient tubular reabsorption of PO_4.

Studies of renal function under intravenous PO_4 load indicates that the tubules respond to the required increase of reabsorption of PO_4 less and for a shorter time than normal. These findings can result either from a further deficiency of the tubules or from a reinforced parathyroid counterregulation.

The meaning of these experimental findings becomes more obvious when compared with the results obtained under and after vitamin D, which will be described in the following report.

FROM THE AUTHORS' SUMMARY.

ENRICHMENT OF MILK WITH VITAMIN D, BY MEANS OF A WATER-SOLUBLE COMPOUND OF VITAMIN D AND LACTALBUMIN. K. HOFMEIER, Lattante **25**:106 (Feb.) 1954.

Milk fortified by a water-soluble preparation of vitamin D and lactalbumin is recommended as very effective in prophylaxis against rickets.

HIGGINS, Boston.

VALUES OF RECALCIFICATION TIME AND PROTHROMBIN TIME AFTER ADMINISTRATION OF FRACTIONATED AND SINGLE DOSES OF VITAMIN E. PAOLO PROSPERI and LORENZO BORSELLI, Riv. clin. pediat. **53**:73 (Jan.) 1954.

The authors have observed in 36 children the behavior of the time of Howell and of the time of Quick, after having administered vitamin E in one or more doses, both orally and intramuscularly, or intravenously, or rectally.

While the time of Quick did not undergo univocal oscillations after such treatment, the time of Howell results were remarkably lowered in all the cases considered, except two, in whatever way the vitamin E was administered.

The authors review what is known through the works of their medical school, upon the relations between vitamin E and hematic coagulation in order to confirm their hypothesis; in fact, they think that vitamin E chiefly activates the thrombokinase, and that the time of Howell is the expression of its action on the process of coagulation.

FROM THE AUTHORS' SUMMARY.

CLEARANCE STUDIES IN VITAMIN D RESISTANT RICKETS. W. RUPP and W. SWOBODA, Monatsschr. Kinderh. **102**:173-175 (Feb.) 1954.

The designation "phosphate diabetes" is justified only if diminished tubular reabsorption of phosphate rather than increased renal phosphate excretion has been demonstrated.

Tubular status regarding phosphate reabsorption can be determined most accurately only by phosphate loading tests.

Concurrent intravenous administration of vitamin D_2 and phosphate solution showed that 1. intravenous vitamin D_2 immediately improved phosphate reabsorption in vitamin-D-resistant rickets, reaching upper limits of reabsorption capacity. This effect decreased markedly after one week. 2. Vitamin D_2 delayed excretion of intravenously administered phosphates. It seems probable that intravenous vitamin D_2 administration represents a better long-term treatment of vitamin-D-resistant rickets than other methods of administration.

HARTENSTEIN, Syracuse, N. Y.

PRIMARY VITAMIN D REFRACTORY RICKETS: I. REPORT OF TWO CASES TREATED WITH HIGH DOSES OF VITAMIN D. J. WINBERG, C. G. BERGSTRAND, B. ENGFELDT, and R. ZETTERSTROM, Acta pædiat. **43**:359 (July) 1954.

Two cases of rickets resistant to vitamin D are described.

The effect of massive doses of vitamin D on calcium and phosphate balance is studied.

This disease is a well-defined clinical entity, and the name "primary vitamin D refractory rickets" is suggested. The nature of the disease is unknown, but it seems likely that the pathogenetic mechanism is different from that in genuine rickets.

FROM THE AUTHORS' SUMMARY.

ACUTE HYPERVITAMINOSIS. A. C. HOOFT, Maandschr. kindergeneesk. **22**:271 (Aug.) 1954.

In four breast-fed infants, 4, 4½, 5½, and 6 months old, respectively, a protruding fontanelle was found following the administration of a large dose of vitamin A (100,000 units of vitamin A and 100,000 units of viamin D; 100,000 units of vitamin A and 600,000 units of vitamin D; 200,000 units of vitamin A and 300,000 units of vitamin D; 100,000 units of vitamin A and 600,000 units of vitamin D).

In three of these infants, the vitamin content of the blood was determined. This was normal in two of the children; in one of them it was considerably raised. In this latter case, the blood was examined 24 hours after the administration of the vitamin A; in the two other infants, 48 hours afterward. It is probable that the passing hypervitaminemia, the patients' ages, the nature of the preparation used, the absorption in the gastrointestinal tract, and the reactivity of the liver and the reticuloendothelial system are important factors in the causation of acute hypervitaminosis A.

FROM THE AUTHOR'S SUMMARY.

Hygiene; Growth and Nutrition; Public Health

TRENDS IN MATERNAL AND PERINATAL MORTALITY IN NEW YORK CITY. HELEN M. WALLACE, EDWIN M. GOLD, LEONA BAUMGARTNER, MARGARET A. LOSTY, and H. RICH, J. A. M. A. **155**:716 (June 19) 1954.

The New York program from 1944 to 1951 has accomplished a reduction in maternal mortality. Also it has accomplished a reduction in neonatal mortality attributed to birth injury, congenital malformations, and gastrointestinal disease. There has been no change in the incidence or weight distribution of prematurity.

KIMBALL, Evanston, Ill.

THE INFLUENCE OF NUTRITION ON THE GROWTH RATE IN THE FIRST YEAR OF LIFE OF CHINESE INFANTS BORN IN SINGAPORE IN 1951. JEAN MILLIS, M. J. Australia **1**:322 (Feb. 27) 1954.

Studies of 103 Chinese infants revealed that those who were wholly or partly breast fed gained better for the first six months than artificially fed infants. After six months no advantage was noted in the breast-fed group.

Breast-fed infants rated higher in the examination at one year. Also, after the fifth month, morbidity in artificially fed infants was notably higher and coincided with the slower rate of growth observed.

Diet of most infants was deficient in vitamin C, though no scurvy was noted.

McGUIGAN, Evanston, Ill.

INFANT MORTALITY IN THE URBAN AFRICAN. LAURA LONGMORE, South African M. J. **38**:295 (April 3) 1954.

Clinics and hospitals are available to the urban African, but only one-third of the babies are taken regularly to them. Most urban Africans believe in witchcraft and medicine men and follow their ancient tribal customs. Because of their suspicion and mistrust of European doctors, the infant mortality rate is very high.

McGUIGAN, Evanston, Ill.

PERINATAL MORTALITY AND MATERNITY HOME HELP IN THE NETHERLANDS. J. H. DEHAAS, Études néo-natal. **3**:71 (June) 1954.

The Netherlands enjoy a unique combination of favorable mortality figures together with a relatively high birth rate.

Holland is the classic country of domiciliary deliveries. Slightly more than 20% of the total number of births (240,000) take place in the hospital. The organization of maternity home-help is more than 25 years old, but has functioned only 10 years in its persent form. After a rapid increase in the postwar years, more than 150 centers of maternity home-help now cover one-forth of the total number of births and one-third of the total number of home deliveries.

Maternity home-helps have a twofold task, to take care of the mother and the newborn child and to substitute for the mother in the household, To take maternity home-help in the family actually means a mental selection. Family traditions have to be overcome and financial sacrifices to be made, the average income being more or less the same as the average in the country. No medical selection takes place compared with the group of home deliveries without maternity home-help.

The preliminary figures of 1949 and 1950, covering 85,000 maternity home-help attendances, are confirmed by the results of 107,000 attendances in 1951 and 1952.

The total stillbirth rate in Holland is still 18 per 1,000 births. Forty per cent of the stillbirths take place in the hospital. The stillbirth rate among the home deliveries without maternity home-help is 15 and among the maternity home-help group 11.2 per 1,000 births. This difference could be largely explained by mental selection, the organization of maternity home-help only slightly contributing to this difference.

The first-week mortality rate in the whole country is 13.8 per 1,000 live births. The first-week mortality among the home deliveries without maternity home-help is 15 to 17 and among the maternity home-help group only 8.9 per 1,000 live births. The simple fact that maternity home-help is given nearly halves the first-week mortality, reducing the rate by about 6 to 8 per 1,000, a striking example of the influence of a general public health measure in attaining a special goal. The greater tendency to hospitalization of the sick newborn in the first week after confinement at home seems to be a credit to maternity home-help to lower neonatal mortality.

The total perinatal mortality in the country is 32 per 1,000, 1 in 30 births! Excluding hospital deliveries, the children delivered without maternity home-help have a perinatal mortality of about 30 and in the maternity home-help group of only 20 per 1,000 births.

Differences in parity have no appreciable influence upon the outspoken differences in perinatal mortality between the two groups of home deliveries. Maternity home-help gives adequate care to the child from the first moment after birth onwards, which is of paramount importance for the

premature and debilitated baby. Stillbirth rate, first-week mortality, and perinatal mortality in the maternity home-help group are even somewhat lower than in the best social group in Amsterdam.

The controversy of hospital versus domiciliary deliveries is a simplification of a complicated problem, to be approached in accordance with traditions, medical facilities, and social habits in every region or country.

The organization of maternity home-help being far from perfect the results can still be improved. These results reach much further than mortality figures can suggest. Planning the stillbirth rate in the next 5 to 10 years between 10 to 15 per 1,000, the first week mortality between 8 to 10, and therefore reducing the total perinatal mortality from 30 to 35 to 20 to 25 per 1,000, combined with a total infant mortality of about 15 per 1,000, is a realistic policy in social obstetrics and social pediatrics in the Netherlands, attainable by simple, nonspectacular, prenatal, natal, and postnatal measures.

FROM THE AUTHOR'S SUMMARY.

A NEW METHOD FOR GRAPHIC RECORDING OF GROWTH. M. LELONG, R. JOSEPH, P. CANLOTBE, and R. SCHOLLER, Presse méd. Supp. 33, p. 701 (May 5) 1954.

The authors describe their personal method for graphic records of the growth in children, which is based on the observation of the whole of the measurements in percentage of deviation as compared to normal averages. Measurements selected for representing the infantile morphology were as follows: cranial, thoracic, abdominal perimeters, bihumeral and bitrochanterian diameters, ratio between the upper and lower segments of the body, and, of course, the height and weight, which remain the two basic data. Such measurements are compared with normal averages for a child of the same age in regard to the height, with the averages for a child of same height in regard to all other measurements (likewise to the osseous and mental age). These average figures are steadily provided by the author's somatograph in merely displacing two couples of cursors over the various curves of body development as designed in Engelbach-Wilkin's fashion. Deviation in percentage is read by the junction on the abaci designed by the authors, of two points corresponding, one to the measurement of the examined child, the other to the correspondent theoretical measurement. The 0% represents the mean normal development; on either side there is physiological varying zone running from —8% from 5 years to 12 years of age, and from —12% up to puberty. The growth is graphically recorded, at an age given, by the morphogram and by the growth curves during the course of years. These documents, being settled in percentage, make it possible to compare the child with himself at the successive ages, and the growth speed of the child is exactly shown by the slope of this growth curve.

Some instances are exhibited concerning congenital myxedema, early puberty, pituitary nanism, retardation genetic in nature.

This new instrument is designed for facilitating the study of those problems on normal and pathologic growth and particularly those problems, still unsolved, concerning auxology.

FROM THE AUTHORS' SUMMARY.

THE CLINIC OF DIMINISHED GROWTH. HANS W. KIRCHHOFF, Med. Klin. **49**:842 (May 21) 1954.

Different forms of deficient growth are discussed on the basis of observations of 50 children. The striking similarities in phenotype and clinical picture of the different forms of diminished growth are said to allow their differentiation.

AMBERG, Rochester, Minn.

HEIGHT AND WEIGHT OF SCHOOLBOYS AT A STOCKHOLM SECONDARY SCHOOL, 1950, AND A COMPARISON WITH SOME EARLIER INVESTIGATIONS. ERNEST ABRAMSON and EVA ERNEST, Acta pædiat. **43**:235 (May) 1954.

During the past 70 years, schoolboys in Stockholm have increased about 15 cm. in height and about 12 kg. in weight, while the increase in height of the adult population is scarcely half as great. No relation between family income and the weight of boys could be shown. A slight connection between the income and increase in height cannot be ruled out. A significant correlation

is to be found between height and social class. The probable reasons for this are discussed. Some relevant research problems, deemed to be of a particular interest, are briefly outlined.

FROM THE AUTHORS' SUMMARY.

Prematurity and Congenital Deformities

INFANT SURVIVAL IN PREMATURITY. E. W. CARTWRIGHT, California Med. **80**:398 (May) 1954.

Reduction of neonatal mortality and the rate of stillbirth may be expected from improved management of spontaneous labor and delivery. Neither roentgenographic measurement, nor the inception of fetal movement or heartbeat, nor any other single test is an index of fetal maturity; all must be considered together.

Prenatal care, particularly, supplemented diet, will help to avoid premature delivery, or at least to prolong pregnancy; since the fetus undergoes accelerated growth during the last weeks of pregnancy, even slight extension of gestation increases the chances for survival.

Analgesia in the first stage of premature labor is contraindicated. Only low spinal anesthesia and other types of conduction anesthesia should be employed for later stages.

The fetal membranes should be preserved as long as possible, but premature rupture does not call for immediate termination of pregnancy. Deep episiotomy and prophylactic outlet forceps are routinely employed to hasten the second stage of premature delivery and to protect the immature fetus. Breech presentation is managed by unassisted expulsion or by forceps extraction of the head.

The umbilical cord is not immediately severed on delivery; administration of oxytocic drugs after the second stage of labor, combined with gentle stripping of the cord, results in rapid transfer of increased amount of placental blood. The airways of the infant should be immediately cleared. Artificial respiration may be necessary, and it must be gentle.

All premature infants should receive supplementary oxygen to render breathing regular and more efficient. They should be insulated immediately in controlled temperature and humidity, and they should be handled little.

PRYOR, Redwood City, Calif.

NEPHROTIC SYNDROME IN A NEONATAL PREMATURE INFANT. R. M. EIBEN, J. KLEINERMAN, and J. C. CLINE, J. Pediat. **44**:195 (Feb.) 1954.

This is a case report. This particular case report concerns a premature Negro baby boy who was placed in an incubator with increased oxygen immediately after birth. He was given menadione, 2.5 mg. intramuscularly twice a day for three days. On the fifth day of life the infant developed signs of respiratory distress, with sternal retraction and cyanosis. Penicillin procaine and streptomycin were then started intramuscularly. A nebulizer was used to increase the humidity within the incubator. The following day the infant developed edema. The edema persisted. The infant developed clinical and laboratory signs of nephrosis.

Corticotropin (ACTH) therapy resulted in temporary clinical improvement. However, the infant devedoped bronchopneumonia and died on the 103d day of life. The final anatomical diagnoses were as follows: (1) lipoid nephrosis, (2) bronchopneumonia, right, (3) acute bronchitis and bronchiolitis, (4) cholelithiasis and choledocholithiasis, and (5) ascites.

The authors believe that this is the earliest reported appearance of nephrosis. They contend that this case supports the idea that lipoid nephrosis is a disease of the infant and young child separate and distinct from the nephrotic phase of chronic glomerular nephritis.

MACDONALD, Pittsburgh.

PROGERIA: REPORT OF A CASE WITH POST-MORTEM FINDINGS. LEONARD ATKINS, New England J. Med. **250**:1065 (June 24) 1954.

A case of progeria (Hutchinson-Gilford syndrome), believed to be the 23d in the literature, is described with autopsy findings. This child survived to the age of 11 years 3 months, when death resulted from severe coronary artery disease with myocardial infarction.

In this case, as well as in another previously autopsied, there was a slight decrease in the number of eosinophile cells of the anterior lobe of the hypophysis. The significance of this is not fully understood. The etiology of the disease is as yet unknown.

SEYMOUR E. WHEELOCK, Denver, Colorado.

CONGENITAL DEFORMITIES OF THE FOOT IN CHILDHOOD. C. F. FERCIOT, Northwest Med. **53**:34 (Jan.) 1954.

The author discusses briefly the current theories related to congenital abnormalities in general and congenital deformities of the feet in particular. He describes congenital clubfoot and flat foot, emphasizing the need of early recognition and treatment. He outlines the stages of development of the untreated deformities, emphasizing the permanent bony and ligamentous deformities secondary to the primary muscular imbalance that, early, lends itself to easy correction.

DOCTOR, Seattle.

DISTURBANCES OF MITOTIC PROCESSES AND TERATISM. D. G. STEYN, South African M. J. **28**:1 (Jan. 2) 1954.

The author points out that the majority of fetal deaths and malformations are due to causes other than heredity, and that proper investigation of vitamins A, B_2, B_{12}, folic acid, riboflavin, and pantothenic acid shows they can cause malformations. So also can maternal hemorrhage or illness or any conditions inducing anoxia in the fetus. Chemical substances which interfere with mitosis can also be a factor. Cortisone, for example, can cause harelip or cleft palate.

The author suggests that investigation should be concentrated in the sixth to eighth weeks of fetal life, and emphasizes the possible role of chemical contraceptives and drugs used during pregnancy. Attention should also be paid to synergists of mitotic poisons.

McGUIGAN, Evanston, Ill.

ACTION OF INGESTION OF PLASMA THROMBIN ON THE CLOTTING TIME IN PREMATURE NEWBORN INFANTS. H. PIGEAUD, H. GABRIEL, BARBAUD, and T. CHANDLIER, Presse méd. Supp. 11, pp. 225 (Feb. 13) 1954.

The authors had previously demonstrated that the ingestion of plasma thrombin is effective on the clotting-time in the newborn infant. They report in the present paper 14 further cases concerning debilitated and premature infants; all of them weighing under 2,500 gm. were given by mouth one or two ampules of plasma thrombin daily for the first five days after birth.

Administration of a single daily ampule is enough to prevent the increase of clotting-time as normally observed after the third day. Two daily ampules are more effective and produce, during the first five days, a diminution in the clotting-time as initially observed, rising to 35% on an average. With some reservation regarding those debilitated or premature infants weighing less than 1,500 gm. and swallowing with difficulty the smallest amount of fluid during the first 24 hours and for whom the treatment should be given only on the second day, the authors are led to state that they gained from the use of plasma thrombin in premature infants as beneficial results as in those of normal weight delivered in breech presentation or by application of obstetrical forceps. They, therefore, strongly advocate the use of plasma thrombin in premature infants in the dose of two ampules a day for the first five days of life as a preventive measure against hemorrhage of the newborn, the high incidence and, perhaps, the severity of which may possibly originate from retarded coagulation.

FROM THE AUTHORS' SUMMARY.

HISTOLOGICAL STUDY OF THE INTRAMURAL NERVOUS PLEXUSES IN A CASE OF MULTIPLE CONGENITAL MALFORMATIONS OF THE ILEUM IN A PREMATURE INFANT. C. IMPERATO and A. MAZZELLA, Lattante **25**:1 (Jan.) 1954.

A twin newborn infant, weighing 1,640 gm., had multiple stenosis of the ileum. A resection of the bowel was done on the fourth day. The child died on the 11th day.

Sections of the intestines were studied histologically. While Meissner's plexus appeared normal, the fibers of Auerbach's plexus showed abnormalities in the areas of the intestine which were stenotic.

HIGGINS, Boston.

THE REFLEXES OF THE IMMATURE AND THE PREMATURE NEWBORN INFANT. I. LONGO and A. VIANELLO, Lattante **25**:149 (March) 1954.

Fifty immature and premature newborn infants were examined as to their reaction to 18 reflexes, those commonly used in clinical tests, on the 1st, 5th, 15th, 30th, 45th, and 60th day of life. In general, the results of these tests did not differ much from those obtained with normal newborn infants. The reflexes of defence and medullary automatism were all present and even more accentuated than are found in normal infants. The tendon reflexes were exaggerated, ankle clonus often being elicited; the more precocious the infant, the less active these reflexes were, as would be expected, as these infants have developed more cortical control. If an immature infant shows a generalized hypotonia, there is probably a pathological defect.

HIGGINS, Boston.

AN UNUSUAL CASE OF HYPOPLASIA OF THE MUSCLES OF THE ABDOMINAL WALL ASSOCIATED WITH MULTIPLE MALFORMATIONS. G. SANSONE and G. SARDINI, Minerva pediat. **6**:109 (Feb. 28) 1954.

A boy 21 months of age presented the typical syndrome of congenital agenesis of the muscles of the abdominal wall and malformations of the genitourinary tract. In addition, this patient had numerous other abnormalities, including mental and physical retardation, marked laxity of the joints, strabismus, nystagmus and cloudiness of the cornea, and abnormal position and function of the large intestine. The etiogenesis of this condition must have been quite early in embryonic life.

HIGGINS, Boston.

INFECTION IN THE PREMATURE INFANT. HUMBERTO GARCES, RAQUEL MUNOZ, and FELIPE FERNANDEZ, Rev. chilena pediat. **25**:109 (March) 1954.

The experience shown is that which is obtained as to infection in the premature infant in the hospital "Roberto del Pio." In a period of 13 years, 547 cases are collected, out of which 80.07% presented infection at some time during their hospital stay. The death rate was 26.87%. In the group of the infected the death rate was double that of the group not infected, which shows the striking importance of infection as the cause of death in these children. The high incidence of death is justified because the children arrive late at the hospital with some form of infection which led to hospitalization and the infection was so serious that the 36.73% of the ones who died did so before 48 hours from the time of admission. An anatomoclinical study is made of the different locations of infection in the premature infant, and those most frequently observed in this material are the following: skin diseases, omphalitis, conjunctivitis, stomatitis, otitis, bronchitis and bronchopneumonia, pleural empyema, pericarditis, diarrhea, peritonitis, meningitis, arthritis, pyuria, sepsis, congental syphilis, tuberculosis, and acute contagious diseases.

In the treatment of the infection, the use of the antibiotics and chemotherapy is considered. Finally, the fundamental rules of its prophylaxis are reestablished.

FROM THE AUTHORS' SUMMARY.

MULTIPLE CONGENITAL ARTHROGRYPOSIS. HUMBERTO GARCES and FERNANDO DONOSO, Rev. chilena pediat. **25**:181 (April) 1954.

A case of arthrogryposis multiplex congenita in a newborn baby (diagnosis made in the second day of his life) is reported. It seems to be the first one published in Chile.

In connection with this case, a review of the literature about this infrequent disease is made.

FROM THE AUTHORS' SUMMARY.

CHLORAMPHENICOL IN INTERSTITIAL PNEUMONIA OF PREMATURE INFANTS. ROLF SCHMÖGER, Deutsche med. Wchnschr. **79**:1051 (June 25) 1954.

Treatment of interstitial pneumonia of premature infants was given to 50 patients, while 50 served as controls. Of the so-treated cases, 40 recovered, while without treatment, only 25 recovered.

AMBERG, Rochester, Minn.

APPEARANCE OF THE FUNDUS OCULI IN PREMATURELY BORN INFANTS TREATED WITH AND WITHOUT OXYGEN. A. HUGGERT, Acta pædiat. **43**:334 (July) 1954.

The author has compared a group of 121 prematurely born children (5 with a birth weight at the highest of 1,300 gm.) who received a large supply of oxygen, with another group of 44 prematures (2 with a birth weight at the highest of 1,300 gm.) who received oxygen to a very slight extent. In the first group, two cases of cicatricial retrolental fibroplasia developed, in the latter group none, while acute peripheral retinal changes of a more pronounced degree occurred among 33 and 4 children, respectively. No definite increase in mortality could be proved to occur among the children as a result of the more restricted use of oxygen.

Very narrow vessels in different parts of the eye, together with pale papillae, were seen during the continuous use of oxygen, while dilated vessels and edema of the fundus oculi certainly occurred more often in children who received oxygen, but these changes did occur also in other cases. In those cases, dilated vessels were often seen immediately after birth or in relation to a lowered general condition, especially if associated with infections.

Oxygen administration is only to be recommended in cases of pronounced asphyxia; at the same time, the importance of a gradual withdrawal of oxygen and control examination of the fundus oculi is stressed in these cases.

FROM THE AUTHOR'S SUMMARY.

INFANTS OF DIABETIC MOTHERS: I. FOETAL HYPOXIA IN MATERNAL DIABETES. G. BERGLUND and R. ZETTERSTROM, Acta pædiat. **43**:372 (July) 1954.

The clinical and pathological features in newborn infants of diabetic mothers are in many respects the same as those in hemolytic disease of the newborn. The abnormally high level of nucleated red cells in the blood must be the consequence of increased erythropoiesis. This is assumed to be caused by an attempt of the fetus to raise its oxygen-carrying capacity. The finding that the oxygen content in the umbilical vein is lower than in control pregnancies seems to give support to this hypothesis.

FROM THE AUTHORS' SUMMARY.

Newborn

POSTMATURITY WITH PLACENTAL DYSFUNCTION. STEWART H. CLIFFORD, J. Pediat. **44**:1 (Jan.) 1954.

Next to prematurity, postmaturity is the most important factor in fetal and neonatal mortality in primipareous women. Stewart Clifford describes the physiologic changes that occur in utero in these infants.

Postmaturity is a particular problem of the first pregnancy—especially when the mother is over 26 years of age. These are the ones that may have trouble. In this problem of postmaturity, the author assumes that the placenta undergoes premature senile degeneration.

The clinical findings in postmature infants are as follows:

First stage: The skin shows loss of vernix. It is dry, cracked, parchmentlike, or peeling, but is unstained by meconium. The infant is long and thin and shows evidence of loss of weight recently in utero.

Second stage: Characterized by the changes mentioned but to a more marked degree and, in addition, signs of intrauterine anoxia with liberation of meconium. Amniotic fluid, placental membranes, umbilical cord, and skin are stained green.

Third stage: A continuation of the second stage but with the passing of time the skin, nails, and cord are stained a marked yellow.

MACDONALD, Pittsburgh.

THE TREATMENT OF ERYTHROBLASTOSIS FETALIS WITH REPLACEMENT TRANSFUSION. FELIX FELDMAN, H. C. LICHTMAN and VICTOR GINSBERG, J. Pediat. **44**:181 (Feb.) 1954.

The authors treated 106 cases of erythroblastosis fetalis with exchange transfusion. There were seven deaths, with a mortality of 6.6%.

The indications for replacement transfusion are a positive Coombs test on cord red blood cells, cord blood hemoglobin level below 15.5 gm., and development of jaundice, pallor, hepatosplenomegaly within the first 24 hours of life. If it is done at all, replacement transfusion should be done within 24 hours after birth to insure the best results.

MACDONALD, Pittsburgh.

HYPOPLASTIC ANEMIA FOLLOWING EXCHANGE TRANSFUSION FOR ERYTHROBLASTOSIS FETALIS ASSOCIATED WITH ISOIMMUNIZATION TO BLOOD GROUP FACTOR "A." E. ALBERT MOODY, J. Pediat. **44**:244 (March) 1954.

Moody reports a newborn infant who developed a regenerative anemia following successful treatment of erythroblastosis fetalis due to isoimmunization of the mother by the fetal blood agglutination "A." There was prompt red blood cell regeneration after the use of oral cortisone.

MACDONALD, Pittsburgh.

SKIN CARE OF THE NEWBORN INFANT. M. M. PENNOYER and M. P. SULLIVAN, J. Pediat. **44**:258 (March) 1954.

Pennoyer and Sullivan explore the relation of various factors that might contribute to an increase in skin infections in babies in a newborn nursery. They point out that in evaluating statistics such as theirs, one must realize the importance of the following factors: longer hospital stay for private white patients, the gradual increase in nursery population in recent years, and the fact that there is an ever-increasing dependence on a shifting nonprofessional personnel in hospital nurseries. Thus qualified, they report that pHisoderm (oily) is a benign hypoallergenic substance and that spraying it on the trunk of the newborn and lathering it into the body by hand on the third day of life is a practical method for reducing the incidence of skin infections in a newborn nursery.

MACDONALD, Pittsburgh.

CLAMPING OF THE UMBILICAL CORD: ITS EFFECT ON THE PLACENTAL TRANSFUSION. ANTHONY E. COLOZZI, New England J. Med. **250**:629 (April 15) 1954.

The fetal-placental circulatory physiology is briefly reviewed.

A study of four techniques of cord clamping and their effect on the blood of 100 normally delivered infants is presented. Cord stripping is considered the most efficacious method of improving the infant's blood picture, with delayed clamping next in preferance. Immediate clamping, by far the worst method, deprives the infant of blood.

Cord clamping apparently has no influence on the weight or general well-being of the normal infant delivered without obstetric complications. Such an infant can adjust itself adequately to a moderate anemia. Conversely, it is apparently no better off, at least clinically, with an increased amount of blood.

Cord stripping or delayed cord clamping or both are urged to effect a maximum placental transfusion in infants who are shocked after a traumatic delivery, anemic after a bleeding accident before or during birth, delivery by Caesarean section, or born prematurely.

WHEELOCK, Denver.

MALNUTRITION OF THE NEWBORN SECONDARY TO PLACENTAL ABNORMALITIES. WALTER PICK, New England J. Med. **250**:905 (May 27) 1954.

Three infants are described who at birth were malnourished, presumably because of an abnormal placenta. Although their birth weight was less than 2,500 gm. (5½ lb.), they were not premature. Their postnatal course differed from that of premature infants in that they regained their birth weight more rapidly, doubled their weight in less than 10 weeks, and were indistinguishable from full-term infants at the age of four to six months.

These malnourished infants are discussed in relation to Clifford's "postmaturity syndrome," and the view is advanced that postmaturity may be one of several etiologic factors that may produce a malnourished infant through an abnormal placenta.

A plea is made to examine the placenta after delivery so that more can be learned about the relation of the placenta to the nutritional status of the newborn.

WHEELOCK, Denver.

WHY SOLID FOODS FOR NEWBORN? FRANK H. DOUGLASS, Northwest Med. **52**:832 (Oct.) 1953.

Answering the question of his title in a negative way, the author reviews the familiar contraindications to the early introduction of solid foods for newborn children and infants.

DOCTOR, Seattle.

ASPHYXIA IN THE NEWBORN. WILLARD F. GOFF, Northwest Med. **53**:32 (Jan.) 1954.

The author presents in outline form the procedures available in resuscitation of the asphyxiated newborn—those procedures recommended, frequently useful, occasionally useful, and contraindicated.

DOCTOR, Seattle.

EFFECT OF SUPERSATURATED ATMOSPHERES ON INSENSIBLE WATER LOSS IN THE NEWBORN INFANT. DONOUGH O'BRIEN, JOHN D. L. HANSEN, and CLEMENT A. SMITH, Pediatrics **13**:126 (Feb.) 1954.

A series of observations are reported which were designed to show the effect of supersaturated atmospheres on the insensible water loss in the normal newborn infant without oral intake. The following conclusions were reached: (1) Supersaturated atmospheres will reduce the insensible water loss in the newborn infant. (2) Under ordinary nursery conditions, this reduction is apparently limited to the insensible water loss from the lungs. (3) The associated economy in body water is in most cases sufficient to prevent the hemoconcentration normally occurring by 72 hours after birth in other infants without oral intake, but not in mist.

FROM THE AUTHORS' SUMMARY.

CAUSES OF STILLBIRTHS AND NEONATAL DEATHS. C. RATNAVATI and D. J. REDDY, J. Indian M. A. **22**:7265 (April) 1953.

The authors analyze 162 stillbirths and neonatal deaths. Of the 162 infants, 47% were premature. Careful study of the obstetric history and clinical and autopsy findings failed to show a cause of death in only eight cases.

Thirty-eight per cent of the fetal and neonatal mortality was caused by maternal complications, like toxemia, hemorrhage, placenta praevia, rupture of the uterus, maternal syphilis, or prolonged labor. Obstetric maneuvers were at fault in only nine cases.

Causes of death in order of frequency were asphyxia; pneumonias; intracranial, renal, or adrenal hemorrhages; congenital malformations, and maternal syphilis.

MCGUIGAN, Evanston, Ill.

CAN WE MAKE A PROGNOSIS FOR THE CHILD FROM THE RH ANTIBODIES OF A PREGNANT WOMAN? N. NORDMEYER, Deutsche med. Wchnschr. **78**:102 (Jan. 16) 1953.

It has been claimed that a high antibody titer, the presence of blocking antibodies earlier than 10 weeks ante partum at repeated examinations, and ABO compatibility of mother and child means an absolutely unfavorable prognosis. This opinion cannot be maintained. An example is given in which in spite of the presence of these criteria, which prompted Caesarean section, an Rh-negative healthy baby was born.

AMBERG, Rochester, Minn.

ELECTROENCEPHALOGRAPHIC FINDINGS IN CHILDREN PREVIOUSLY TREATED FOR ASPHYXIA NEONATORUM. M. D'AVIGNON and I. KEILSON, Acta pædiat. **42**:407 (Sept.) 1953.

On follow-up examination of 61 children subjected to postnatal treatment for asphyxia neonatorum in the newborn period, 44 disclosed electroencephalographic changes. Grave pathologic findings were noted only in children who, at the follow-up, showed somatic and mental defects (14), while children with slight electroencephalographic changes (16) have developed well in all respects, up to the age at which the follow-ups were performed, in spite of a neonatal asphyxia. The neonatal asphyxia in the last-mentioned cases is supposed to have produced organic cerebral injuries of such a degree or nature as to disclose no clinical, but simply electroencephalographic, changes.

FROM THE AUTHORS' SUMMARY.

HYPOCALCEMIA IN THE NEWBORN. C. SMEENK, Maandschr. kindergeneesk. **21**:122 (April) 1953.

The author describes four cases of hypocalcemia and one of probable hypocalcemia in the neonatal period. The symptoms were convulsions, attacks of cyanosis, paralytic ileus, and scleredema.

There also were three older children, seriously ill with infections, who had hypocalcemia; they recovered after parathyroid hormone therapy.

FROM THE AUTHOR'S SUMMARY.

Acute Contagious Diseases

A Study of the Relationship of the Absence of Tonsils to the Incidence of Bulbar Poliomyelitis. Louis Weinstein, Martin L. Vogel, and Norman Weinstein, J. Pediat. **44**:14 (Jan.) 1954.

Patients who have had their tonsils and adenoids removed are more susceptible, when they contract poliomyelitis, to the bulbar and bulbospinal forms of the disease than those who still possess these lymphoid structures. This decreased resistance to the more serious types of infection is not related to the time at which tonsilladenoidectomy was carried out and is not influenced to any significant degree by age or sex. The authors, on the basis of a study of 800 cases of poliomyelitis, sustain this idea, which had previously been reported by others.

The total number of patients in these three investigations is 3,179. The conclusion is as follows: The increased susceptibility to the bulbar form of poliomyelitis after recent removal of the tonsils suggests that the time of tonsillectomy in relation to the onset of poliomyelitis may be of less significance than the mere fact that the tonsils are absent.

Macdonald, Pittsburgh.

Studies on Viremia in Poliomyelitis. C. W. Jungeblut and E. J. Huenekens, J. Pediat. **44**:20 (Jan.) 1954.

Blood samples were obtained from 22 patients during the acute stage of paralytic poliomyelitis. Active virus was isolated from the blood of one patient. However, the authors agree that their failure to obtain active virus in more cases might have been caused by technical difficulties. They support the idea that in the early paralytic stages of poliomyelitis in man there is a viremia.

Macdonald, Pittsburgh.

The Infrequent Incidence of Nonparalytic Poliomyelitis. E. B. Shaw and Marcia Levin, J. Pediat. **44**:237 (March) 1954.

Shaw and Levin say that by and large clinically recognizable poliomyelitis is invariably followed by detectable muscle weakness. Mild degrees of paralysis may be found only by careful examination and follow-up study, but the detection and adequate treatment of minor paralysis may prevent significant late sequalae. They emphasize careful examination and follow-up. In their series of 798 consecutive cases of poliomyelitis, only 3.9% were nonparalytic, compared with a nonparalytic rate of 31.2% for their state of California over a comparable period as reported by Public Health Agencies. To repeat, they say that careful examination of the patient with poliomyelitis will demonstrate muscular weakness in all but a few and that the recognition of this may prevent sequelae.

Macdonald, Pittsburgh.

The Rubella Problem. Saul Krugman and Robert Ward, J. Pediat. **44**:489 (May) 1954.

There is in these times an anxiety, almost hysteria, about rubella in the first trimester of pregnancy. It started in Australia. In 1941 Gregg reported congenital cataract following rubella in the mother, and this historic report was followed by a study of Swan and others relating maternal rubella to cataract, deaf-mutism, heart disease, and microcephaly in the child.

Krugman and Ward have attempted to clarify the clinical picture of rubella. Except in epidemics, it may be a difficult diagnosis. They attempted to evaluate the effect of gamma globulin in prevention. Neither ordinary nor convalescent gamma globulin is consistently effective in the prevention of rubella. There is some evidence that gamma globulin may modify the disease. They attempted to estimate the risk of congenital malformations in the newborn. It is impossible to give a precise figure for the risk involved following rubella acquired during the first trimester of pregnancy. From available statistics the risk is somewhere between 10 and 90%. The low percentages are Swedish, the high percentages Australian.

The risk following infection during the second and third trimesters of pregnancy does not appear to be significant.

What should the doctors do? Gamma globulin may help or may not. Statistics are equivocal. Therapeutic abortion is an individual problem for the physician and his patient.

Macdonald, Pittsburgh.

POLIOMYELITIS: SPREAD AND CONTROL. D. M. DAYTON, Northwest Med. **53**:143 (Feb.) 1954.

The author revives a hypothesis set forth by Toomey and August, in 1933, that the perishable fruits of the temperate zones might have some causative relation to the spread of poliomyelitis.

In the light of present-day knowledge of poliomyelitis, the supposed methods of transmission, the seasonal and climatic distribution of epidemics, and the possible role of the fruit fly as a vector, the author presents "evidence" incriminating the soft perishable fruits and the unsanitary itinerant fruit picker. He decries the apparent lack of interest in current research along this line, and makes a plea for public health measures and education to enforce decent sanitation in the handling of perishable fruit as a means of preventing the epidemics of poliomyelitis occurring during the harvest peak.

DOCTOR, Seattle.

A LOCAL STUDY OF EPIDEMIC POLIOMYELITIS. S. P. LEHMAN and G. D. LAVECK, Northwest Med. **53**:250 (March) 1954.

Lehman and LaVeck studied 236 cases of poliomyelitis in King County, Washington, in 1952. Results tend to confirm previous reports that pregnancy, the menstrual cycle, parenteral injections, tonsillectomy, absence from home, and contact with an active case all play a part in epidemiology.

DOCTOR, Seattle.

PERSISTANT OF NEUTRALIZING ANTIBODIES IN HUMAN SUBJECTS THREE YEARS AFTER ORAL ADMINISTRATION OF A RODENT-ADAPTED STRAIN OF POLIOMYELITIS VIRUS. HILARY KOPROWSKI, GEORGE A. JERVIS, and THOMAS W. NORTON, Pediatrics **13**:203 (March) 1954.

The sera of 14 children who were fed the TN strain of poliomyelitis virus (Type II) three years previously showed persistence of high titer neutralizing antibodies.

FROM THE AUTHORS' SUMMARY.

ERYTHEMA INFECTIOSUM: CLINICAL AND EPIDEMIOLOGICAL OBSERVATIONS. I. E. PHILLIPS, South. M. J. **47**:252 (March) 1954.

Clinical features of this disease are red cheeks, lasting one to four days, followed in one to two days by or simultaneously with a diffuse mottled erythema consisting of tiny bright red macules which are noted on the extensor surfaces of the extremities, especially the arms. Treatment is symptomatic, though the author suggests possible value of the corticosteroids. An epidemic in Tennessee is reported. Twenty-four children, ranging in age from 17 months to 13 years, were involved in one year, 4 children in the following year, and 1 in a third year.

Evidence is presented to suggest that the disease is spread to humans by bites from previously infected mites from starlings.

LOGAN, Rochester, Minn.

TREATMENT OF ACUTE PARALYTIC POLIOMYELITIS. S. E. J. ROBERTSON, M. J. Australia **1**:73 (Jan. 16) 1954.

The cardinal principles of treatment are well discussed. Emphasis is laid on the surgeon, anesthetist, and laryngologist; all are needed, as well as experienced nurses and the best possible equipment.

MCGUIGAN, Evanston, Ill.

Diseases of Blood, Heart and Blood Vessels, and Spleen

VALVULAR STENOSIS AS CAUSE OF DEATH IN SURGICALLY TREATED COARCTATION OF AORTA. G. JACOBSON, R. S. COSBY, G. C. GRIFFITH, and B. W. MEYER, Am. Heart J. **45**:889 (June) 1953.

The authors report the death of three patients during or shortly after surgical correction of coarctation of the aorta. Autopsy revealed a complicating cardiac lesion in all three. One had congenital mitral stenosis; another had subaortic stenosis, and the third had a bicuspid aortic valve with calcific stenosis.

The importance of careful search for associated lesions is emphasized, and the authors believe that in the presence of coexisting mitral stenosis, aortic stenosis, or subaortic stenosis operation for coarctation of the aorta is contraindicated.

GIBSON, Chicago.

CAUSES OF ACUTE PERICARDITIS. ROBERT L. REEVES, Am. J. M. Sc. **225**:34 (Jan.) 1953.

A review is presented of the hospital records of 96 patients of all ages for whom the diagnosis of acute pericarditis was made. These patients represented 7% of the total hospital admissions, and the diagnoses were made by adequate conservative criteria, ranging from autopsy findings or positive pericardicentesis to a combination of major and minor physical and laboratory signs. A breakdown of etiological data revealed that rheumatic fever accounted for 40.6% of the cases, purulent involvement for 19.8%, and a variety of causes for the remainder. The electrocardiogram was of diagnostic value in only 38%, while the x-ray revealed changes in 50% of the cases of tuberculous pericarditis and in less than a third of the others. A pericardial friction rub was heard in the vast majority of cases of rheumatic etiology and in over 50% of all other types.

SUTTON, Evanston, Ill.

ANEMIA IN THE RABBIT DURING PREGNANCY AND FOLLOWING TREATMENT WITH WATER-SOLUBLE OVARIAN EXTRACTS. M. X. ZARROW and I. G. ZARROW, Endocrinology **52**:424 (April) 1953.

Anemia of pregnancy has been described in a number of widely divergent species of mammals. In general, it has been concluded that this phenomenon is due to a hemodilution.

The present investigation was undertaken to elucidate the factors responsible for the anemia of pregnancy. In the initial phase of this study, the normal pattern of pregnancy was established by determining the changes in the water balance, the circulating erythrocytes, leucocytes, hemoglobin, hematocrit, nonprotein nitrogen, and chlorides of the blood, and the urinary chlorides. In the second part of this study, the same determinations were made in rabbits during treatment with a water-soluble extract of the ovary of pregnant sows. This preparation (relaxin) was tested in these experiments, since previous work had shown that it possessed the ability to cause water retention and thus possibly produce a hemodilution.

It was concluded that the rabbit develops an anemia of pregnancy concomitant with a water retention.

It was concluded that treatment with the ovarian extract produces a definite retention of water and an anemia similar to that noted during pregnancy.

JACOBSEN, Buffalo.

OXYGEN EQUILIBRIUM OF FETAL AND ADULT HUMAN HEMOGLOBIN. D. W. ALLEN, J. WYMAN JR., and C. A. SMITH, J. Biol. Chem. **203**:81 (July) 1953.

Studies were carried out on hemoglobin solutions prepared from human maternal and cord blood. The lessened affinity for oxygen of fetal hemoglobin noted by previous workers was confirmed.

When the hemoglobin solutions were subjected to dialysis, however, this difference disappeared, and adult and fetal hemoglobin were found to possess equal affinities for oxygen. These findings suggest that the reported differences in oxygen equilibria may be the result of differences in the environment of the hemoglobin molecule rather than of intrinsic differences in the molecule itself.

FORBES, Rochester, N. Y.

INFLUENCE OF FATS AND FATTY ACIDS ON CAPILLARIES. JENO KRAMAR and VICTOR E. LEVINE, J. Nutrition **50**:149 (June 10) 1953.

Kramar and Levine, from their observations, concluded that a fat-deficient diet, lacking in essential fatty acids, may cause the skin capillaries of immature albino rats to become more fragile and more permeable. It was also suggested that fats, and presumably essential fatty acids, are necessary for the physiologic integrity of the skin capillaries of the immature albino rat.

As for clinical significance, testing for capillary resistance in the human being is performed on the skin. For proper evaluation of the findings one must consider the factors known to influence capillary resistance. Among these factors may be mentioned temperature, time of day, season, site of testing, menstrual cycle, and diet, so far as certain vitamins are concerned. Another factor, hitherto not considered, must now be added, that is, dietary fat.

FREDEEN, Kansas City, Mo.

OFFICE DIAGNOSIS OF OPERABLE CONGENITAL HEART LESIONS. ROBERT TIDWELL, ROBERT RUSHMER, and ROBERT POLLEY, Northwest Med. **52**:546 (July) 1953.

This is the first of a series of six one-page, graphically illustrated articles on the office diagnosis of congenital heart lesions. The page is headed by a diagrammatic representation of the fluoroscopic appearance of the normal heart, followed by the fluoroscopic appearance of the congenital abnormality being discussed. The page is completed by a summary of the diagnostic aids available for the office use which should lead to a definitive diagnosis of the heart lesion.

This issue discusses patent ductus arteriosus and is to be followed by discussions of coarctation, vascular rings, auricular septal defect, the tetralogy of Fallot, and tricuspid atresia.

DOCTER, Seattle.

COLORIMETRIC DETERMINATION OF ALBUMIN-GLOBULIN RATIO IN BLOOD SERUM. M. NOVERRAZ, Schweiz. med. Wchnschr. **83**:1092 (Nov. 7) 1953.

The method of determining the albumin-globulin ratio in the blood serum is based on their separation by ammonium sulfate and the determination of the xanthoprotein reaction of the precipitates electrophotometrically. Only 0.2 ml. of serum is required. All the solutions of the reagents are stable, and the color does not change within 24 hours.

AMBERG, Rochester, Minn.

PARADOXICAL CEREBRAL ABSCESSES IN PATIENTS WITH CONGENITAL MALFORMATIONS OF THE HEART. G. SALVIOLI and M. MILLETTI, Clin. pediat. **35**:855 (Dec.) 1953.

A 9-year-old boy with the tetralogy of Fallot developed an abscess in the left frontal lobe; recovery followed surgical intervention.

A search of the literature revealed reports of 80 cases in which patients with congenital heart disease had developed brain abscesses; the earliest report was in 1814. Eight of the 16 patients on whom operation was done recovered. The cardiac lesion in 39 of the patients was the tetralogy of Fallot; practically all the other patients had a septal defect. It is rather surprising that hardly any of the patients had endocarditis.

HIGGINS, Boston.

SO-CALLED PERNICIOSIFORM ANEMIA, WITH MEGALOCYTES, OF CHILDREN. L. CARTAGENOVA, Lattante **24**:856 (Nov.) 1953.

Diagnoses of perniciosiform anemia with megalocytemia were made in the cases of two infants, a boy of 13 months and a girl of 12 months, who presented the picture of hemolytic anemia, megalocytes in the peripheral blood, megaloblastosis in the bone marrow, glossitis, and gastrointestinal disturbances. Favorable results followed treatment with liver extract and vitamin B_{12}. Aside from a few cases described from America, practically all cases previously reported have been from Sicily. The cases described in this paper were from Northern Italy; the children were not of Sicilian parentage.

HIGGINS, Boston.

HEPARIN ACTIVITY OF PLASMA IN SOME PATHOLOGICAL CONDITIONS IN CHILDREN. G. GELLI and D. BIAGINI, Minerva pediat. **5**:820 (Sept. 30) 1953.

The toluidine blue test was used to evaluate heparin activity in the plasma of children with various diseases. No appreciable deviation from normal was found in cases of glomerular nephritis or of tuberculosis under treatment with isoniazid. Only in some cases of leukemia, purpura, or epistaxis was there found an increased heparin activity. The giving of corticotropin or cortisone was found to increase the heparin activity slightly, but only for a few days.

HIGGINS, Boston.

THE REACTION OF THE CHILD'S CARDIOVASCULAR SYSTEM TO COFFEE AND TO COFFEE FROM WHICH THE CAFFEINE HAS BEEN REMOVED. G. GRANATA, Minerva pediat. **5**:915 (Oct. 31) 1953.

Observations were made as to the effect of coffee and of coffee from which the caffeine had been removed (Kaffee Hag) on the respiration rate, the pulse, the blood pressure, and the electrocardiogram of 110 persons, most of them children. The subject was observed first at rest, then after a cup of Kaffee Hag (96% of the caffeine having been removed from the bean), then after a cup of coffee, and finally after another cup of Kaffee Hag. The tests clearly showed that the pharmacological effects of the coffee were due to its caffeine content. A cup of coffee contains from about 0.1 to 0.2 gm. of caffeine. The results showed that the reaction of children to coffee were very similar to that of adults. The most striking effect of the coffee was in the blood pressure findings. There was a rise in blood pressure in practically every subject, the minimum rise in the systolic pressure being 10 mm. of Hg and in the diastolic, 5 mm. of Hg. Some of the children showed a remarkable sensitivity to the coffee; in the seven cases of glomerulonephritis, the rise was from 30 to 50 mm. of Hg. One diabetic child showed a rise in blood pressure from 100/60 to 210/100; a child with a pheocytoma had a rise in blood pressure from 120/50 to 240/120. With the increased systolic response to the caffeine, rhythmic disturbances occurred in some of the children's heart action; extrasystoles and tachycardia were the most commonly found. The pulse rate and the respiration rate both tended to increase, but not to the marked degree of or so consistently as the blood pressure.

HIGGINS, Boston.

MICRODREPANOCYTIC DISEASE. E. SILVESTRONI and I. BIANCO, Pediatria **61**:11 (Jan.) 1953.

Microdrepanocytosis is a relatively severe type of anemia in which there are found red cells of both the microcytic and the sickle types. The sickle cell trait comes from one parent and the microcytic trait from the other parent. Geneological charts are given of 11 families, in which there were at least 26 patients with the disease. The course of the disease is similar to that of Cooley's anemia. Several of the patients have lived to adulthood. One instance is cited in which one father with the disease had 12 children, 4 of whom had proved cases of the disease.

HIGGINS, Boston.

TWO CASES OF ENDOCARDIAL FIBROELASTOSIS IN INFANCY. MAURICE LUST, RENÉ PETIT, and JOUANG SING TSEIN, Rev. españ. pediat. **9**:859 (Sept.-Oct.) 1953.

The authors present two cases of endocardial fibroelastosis with autopsy findings and microscopic sections. They review the theories as to etiology and possible treatment. The clinical symptoms, ECG findings, etc., are described.

ALLEN, Santa Fe, N. Mex.

PELGER'S NUCLEAR ANOMALY IN CHILDHOOD. JOHANNES OEHME, Arch. Kinderh. **146**:155, 1953.

A description of three families with Pelger's nuclear anomaly is given. The significant trait of this anomaly is the incomplete segmentation of the polymorphonuclear leucocytes. The nuclei are smaller than normal and show as a rule only two segments, and the chromatin is pyknotic.

This entity was described first by Pelger in 1930. Several cases are recorded in the literature in which the nuclear anomaly was associated with other hematological diseases and retarded growth. The observation of the author does not confirm the simultaneous occurrence of other abnormalities. The hereditary trait is obviously dominant.

The main clinical significance lies in the fact that a confusion with band forms and a high-grade infection in the differential count is easily possible.

GOTTSTEIN, Chicago.

RETICULOENDOTHELIOSES. PAUL FREUD, Wien. klin. Wchnschr. **65**:219 (March 13) 1953.

A review is given touching on Hand-Schüller-Christian disease, Letterer-Siwe disease, eosinophilic granuloma of the skeleton, and certain forms of xanthomatosis of the skin, in all of which lesions of the reticuloendothelial system prevail. Special consideration is given to a lesion best designated as leukemic xanthomatosis, which has not been described previously.

In a 6-month-old infant a xanthoma disseminatum of the skin existed. One year later the leucocyte count was 140,000 per cubic millimeter, with many myeloblasts. The bone marrow presented leukemic activity. The picture was that of a chronic myelocytic leukemia. A couple of years later, at the biopsy of a lymph node, a beginning reticuloendotheliosis was seen. The child lived three years longer, when a profuse general reticuloendotheliosis was demonstrated. In the tissues numerous inclusion bodies were seen.

AMBERG, Rochester, Minn.

POLYPHENOLOXIDASE ACTIVITY IN MATERNAL AND FETAL BLOOD SERUM. P. ELSNER, O. HORNYKIEWICZ, A. LINDNER, and G. NIEBAUER, Wien. klin. Wchnschr. **65**:938 (Nov. 13) 1953.

Serum of the newborn was obtained, after tying the cord, by recutting. The substrate was pyrocatechol. The method of determination is given. The oxygen consumption was measured in the Warburg apparatus, and in some cases the intensity of the brownish-red color of the Warburg reaction mixture was determined photometrically. The polyphenoloxidase activity of the newborn's blood serum is much less than that of the mother's serum. The placenta forms a barrier which does not allow its passage.

AMBERG, Rochester, Minn.

PRIMARY CARDIAC RETICULUM CELL SARCOMA IN A 16-MONTH-OLD CHILD. P. GILLET and R. PARMENTIER, Acta pædiat. belg. **7**:27, 1953.

The clinical history and autopsy findings in a case of primary reticulum cell sarcoma of the interauricular septum, with invasion of the left auricle and metastases in the pericardium, lungs, and spleen, is described. The authors point out the impossibility of making a clinical diagnosis because of the lack of specific symptoms.

GLASER, Jerusalem.

RARE SYNDROME OF HEMORRHAGIC TENDENCY (AFIBRINOGENEMIA): PRESENTATION OF CLINICAL CASE. E. VAN NUFFEL and M. VERSTRAETE, Acta pædiat. belg. **7**:185, 1953.

The case of 7-day-old boy who first showed signs of a bleeding tendency one day after birth is presented. He was treated with blood and plasma transfusions. No hereditary or other cause could be found for the disease; there was a complete absence of fibrinogen in the blood.

The cases so far reported in the literature are analyzed in table form.

GLASER, Jerusalem.

Diseases of Nose, Throat, and Ear

ENDOTRACHEAL ANESTHESIA FOR TONSILLECTOMY AND ADENOIDECTOMY IN CHILDREN. J. W. PENDER and O. E. HALLBERG, J. A. M. A. **153**:1073 (Nov. 21) 1953.

Pender and Hallberg list the advantages and disadvantages of endotracheal anesthesia with a number of general rules for avoiding trauma during intubation as well as avoiding motion of the tube in the larynx and the utmost importance of using chemically and bacteriologically clean tubes.

They support their views and data with a listing of three tables indicating the exact size of the endotracheal tube with respect to the age of the child (989 cases), the size with respect to the weight of the child (602 cases), and the duration of intubation (1,023 cases).

They conclude that disadvantages of this type of anesthesia have been overemphasized and that the working space of the surgeon is not obstructed, in fact, visualization is improved.

GORDON, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

TECHNIQUE OF REMOVAL OF ADENOID TISSUE OF THE NASOPHARYNX IN CHILDREN. PHILIP E. MELTZER, J. A. M. A. **154**:228 (Jan. 16) 1954.

Meltzer describes a technique for the removal of adenoid tissue of the nasopharynx which has given him the best results in his many years of surgery. It is performed with the patient in an upright position, under endotracheal anesthesia, with the nasopharynx exposed to the view

of the otolaryngologist, so that the adenoidectomy is accomplished under direct visualization. Thus no longer will a "blind" adenoidectomy be performed.

For a fuller description of the technique, the reader is urged to consult the original article.

GORDON, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

TRACHEOTOMY IN INFANCY. JOHN A. BIGLER, PAUL H. HOLINGER, KENNETH C. JOHNSTON, and FILMORE SCHILLER, Pediatrics **13**:476 (May) 1954.

The incidence of tracheotomy in infants under one year of age is increasing due to a broadening of indications, greater acceptance of tracheotomy as an adjunct to other therapy, and a lower mortality through improvements in surgical technique and in the postoperative care of tracheotomized infants.

Tracheotomy for inflammatory lesions is decreasing, but the incidence of tracheotomy for congenital and miscellaneous lesions is increasing.

Of 62 infants under one year of age who required tracheotomy, congenital lesions were considered the cause of the respiratory obstruction in 32 cases (15 boys and 17 girls) and acquired lesions in 30 (21 boys and 9 girls). In 8 of the 30 infants in the "acquired" group, congenital anomalies were indirectly responsible for the tracheotomy, since it was necessitated following extensive surgical procedures performed in an attempt to correct gross anomalies of organs other than those of the respiratory system.

There were 17 deaths in the series of 62 cases. Eight occurred in the miscellaneous group, principally those operated on for gross anomalies of other organs, three in the group of 17 congenital laryngeal anomalies, four in the group of 18 inflammatory lesions, and two in the group of 8 neoplasms.

Tracheotomy is generally looked upon as an emergency life-saving procedure. However, in most cases it can be a planned careful operation, preceded by the establishment of an airway to avoid cerebral and surgical trauma. The post-tracheotomy period is the critical period during infancy.

FROM THE AUTHORS' SUMMARY.

SYMPOSIUM ON HEARING TESTS AND THEIR SHORTCOMINGS. P. F. KING, M. R. DIX, J. D. HOOD, and R. S. DADSON, Proc. Roy. Soc. Med. **46**:991 (Dec.) 1953.

At the meeting of the Otology Section of the Royal Society of Medicine on Feb. 6, 1953, Air Vice-Marshal E. D. D. Dickson presided. Wing Commander King spoke on "Some Imperfections of the Free-Field Voice Tests." Conversational voice should be heard at 20 ft. (6 m.) by the normal ear, but various examiners report different readings. This figure is therefore unreliable. Whispered voice does not depend on vibrations of the vocal cords but is produced by the residual air in the lungs after expiration. Whispered sibilants are heard further than spoken low-tone words. The weaknesses of the test for the whispered voice are failure to standardize the technique; inability to control the pitch and intensity of a whisper; lack of control of "ambient tones." Lack of control of the latter seems common. Tests should be conducted in a quiet room, "sound-damped, having an ambient noise level of 50 db. or less." Test rooms vary in acoustics. Any change in the contents of a room (furniture) changes its transmission characteristics. Reference is made to the Committee on Hearing of the National Research Council, which in 1948 adopted pure-tone audiometry. "In the future, speech audiometry will probaby be used as the basis for hearing standards, and this will be the ideal."

Drs. Dix and Hood, of the National Hospital, Queen Square, London, described "Modern Developments in Pure Tone Audiometry and Their Application to the Clinical Diagnosis of End-Organ Deafness." They state: "There is, at the moment, no degree of standardization in the manner in which the onset of the tone is controlled in any of the commercial audiometers, and they appear to vary greatly."

Mr. R. S. Dadson discoursed on "Some Possible Sources of Error in Audiometry and Their Remedies." He spoke of the physical limitations, the importance of the "reference threshold," and the lack of adequate calibration facilities. In the past there has been no agreement as to the threshold values at different frequencies. Undesirable effects are found in the variability of the coupling between the earphone and the subject's ear. Leakage of sound results from imperfect

sealing between the earcap and the ear. In order to reduce errors the designs of earphones for use with audiometers deserves further study. There are limitations due to bone-conducted sounds and "the mechanical impedance of the mastoid process."

The work done to date has been a part of the research program of the National Physical Laboratory (England).

ABSTRACTOR'S COMMENT: When one considers the years that have gone by and the number of investigators in physical laboratories, its seems about time that some more definite conclusions should be "openly arrived at" and that better standardization, both here and abroad, be established. It may be that recent work on transistors shall bring about a better understanding of aural functions and disabilities.

I. W. VOORHEES, New York [A. M. A. ARCH. OTOLARYNG.].

OBSTRUCTIVE LARYNGITIS IN CHILDREN. JULIO MENEGHELLO, OSCAR UNDURRAGA, and HAYDEE SEPULVEDA, Rev. chilena pediat. **24**:475 (Dec.) 1953.

Obstructive laryngitis is a frequent syndrome in infancy, most frequently due to an infection. Age is a factor in the different etiology; in children over 3 years, old diphtheritic laryngitis is seen oftener, while in those under that age, acute infectious laryngitis is commoner; in the laryngitis that follows measles, there apparently is no age factor. It occurs more often during autumn, winter, and the beginning of spring. The duration of the obstructive symptoms as well as of the fever was generally one week, except in those complicated cases, the cases operated on or the desperate ones. The correct diagnosis was usually made clinically plus the endoscopic study and serial bacteriological examinations. The authors believe that endoscopy done early, that is, at the beginning of the symptoms, is the most important diagnostic guide. Treatment, in any case in which there is doubt, will be diphtheria antitoxin followed by all the measures to relieve the obstructive symptoms, aspiration of secretions, oxygen, and humidity. If with these procedures the obstructive symptoms persist, surgical treatment should be considered. With the systematic use of antibiotics, the authors have not seen a significant modification of the obstructive symptoms, although they favor their use due to the frequency with which there are associated infectious complications. The total mortality was 8.9%.

There were few complications, these being mostly transient paralysis of the vocal cords and subglottic stenosis.

FROM THE AUTHORS' SUMMARY.

Diseases of Lungs, Pleura, and Mediastinum

PULMONARY RESECTION IN THE FIRST YEAR OF LIFE. E. S. CROSSETT and R. R. SHAW, Surg., Gynec. & Obst. **97**:417 (Oct.) 1953.

Six case reports indicate the value of pulmonary resection in infants under one year of age. Congenital pulmonary cysts should be differentiated from pneumothorax and can be successfully removed. Localized hypertrophic emphysema and localized fetal atelectasis not responding to conservative therapy can be treated by segmental or lobar excision. Bronchiectasis associated with fibrocystic disease of the pancreas offers the poorest prognosis, because of the chronic progressive nature of the primary disease. The surgery in infants can be performed with a high degree of safety in these days of improved technique, antibiotic therapy, and increased knowledge of respiratory physiology.

FRIEDBERG, Chicago [A. M. A. ARCH. OTOLARYNG.].

INTERSTITIAL PLASMA-CELL PNEUMONITIS IN INFANTS. G. COLOMBO and E. TAUBER, Minerva pediat. **5**:165 (March 15) 1953.

An epidemic of plasma-cell pneumonitis occurred in a hospital in Turin in the spring of 1952. There were 19 cases in all; the patients were all underweight, four being premature infants. Their ages varied from 2 to 4 months. Ten of the patients died; none of the antibiotic or sulfamide drugs seemed to be specific for the disease. Histological examination of the lung tissue showed a dense infiltration with lymphocytes, plasma cells, and monocytes.

HIGGINS, Boston.

AN EPIDEMIC OF INTERSTITIAL VIRUS PNEUMONITIS. G. ROTTINI and A. DELLA SANTA, Minerva pediat. **5**:202 (March 31) 1953.

The clinical, laboratory, and radiological aspects are recorded of 23 cases of virus interstitial pneumonitis, occurring during an epidemic in Trieste in June 1952. The patients all recovered, although some were not wholly well until the third month of their illnesses. The onset was usually with fever, dyspnea, and cough. The pneumonitis was usually localized in the right lower lobes and was accompanied with enlargement of the hilum glands. In seven of the cases there was a complication of hepatitis with jaundice six to eight weeks after the onset of the pneumonitis. The white blood cell count was under 5,000 in 39% of the cases and over 7,000 in 26%. No pathogenic organisms predominated in throat or sputum cultures.

HIGGINS, Boston.

THE SYNDROME OF LOEFFLER. M. MALASPINA, Minerva pediat. **5**:276 (April 30) 1953.

Löffler's syndrome is pneumonia of unknown etiology but with the characteristics of an allergic disease. A 6-year-old girl developed asthenia, anorexia, headache, vomiting, and diarrhea. Three days later, she had a high fever, a dry cough, and dyspnea; x-ray and physical examinations revealed consolidation of the left lung between the scapula and the spine at the fourth vertebra. The white blood cell count averaged 11,000, with 25% eosinophiles. No intestinal parasites or ova were found in the stools. After five days, respiratory symptoms were gone, and the x-ray picture of the lungs was normal. One month later, there were 10% eosinophiles in the differential white blood cell count.

HIGGINS, Boston.

OIL PNEUMONIA DUE TO ASPIRATION OF LIQUID PETROLATUM. WALTER DONTENWILL, Monatsschr. Kinderh. **101**:35-37 (Feb.) 1953.

A 3¼-year-old white girl with tuberculous meningitis, marked internal hydrocephalus, and a tuberculous lesion of the right femur received daily doses of 1 teaspoonful (4 to 5 ml.) of liquid petrolatum as a laxative for several months before death. Autopsy, in addition to the above tuberculous foci, revealed bilateral oil pneumonia presumed to be due to repeated aspirations of the liquid petrolatum. This is believed to be the only case in the German medical literature up to the present time of oil pneumonia due to aspiration of oily laxatives.

HARTENSTEIN, Syracuse, N. Y.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

HAEMANGIOENDOTHELIOMA OF LIVER SIMULATING CONGENITAL HEART DISEASE IN AN INFANT. C. BLACLAND LEVICK and J. RUBIE, Arch. Dis. Childhood **28**:51 (Feb.) 1953.

A case of hemangioendothelioma of the liver in the neonatal period is described. Dyspnea, feeding difficulty, central cyanosis, a systolic murmur, and a grossly enlarged heart suggested that a congenital heart lesion with heart failure was present. At necropsy no such lesion was found, and the correct diagnosis was established.

KELLY, Milwaukee.

FŒTAL ASCITES. JOSEPHINE M. LORD, Arch. Dis. Childhood **28**:398 (Oct.) 1953.

Two cases are here reported of ascites associated with obstructive lesions of the lower urinary tract. Both patients were boys, one being 5 weeks old when the diagnosis was made and the second newborn. The diagnosis was suspected in the second patient, but, unfortunately, he died of atelectasis before the ascites could be relieved.

A study of the literature shows that ascites may occur in cases of cirrhosis, fetal peritonitis, agenesis of intra-abdominal organs, and imperforation of the anus. Congenital obstruction of the urethra is the commonest cause of fetal and neonatal ascites. Two main types occur. In the first there is an associated malformation of the anus, and the urinary tract abnormality is gross and the prognosis poor. In the second, and apparently commoner, type there is an isolated urethral obstruction in the male, and prompt surgical treatment may be effective. Success in one such case has been reported. Once suspected, the diagnosis is easy to establish, and it is important that this cause of fetal ascites should be recognized.

KELLY, Milwaukee.

BIO-CHEMICAL CHANGES IN DIARRHOEA OF CHILDREN: THEIR INTERPRETATION AND APPLICATION IN THERAPY. K. C. CHAUDHURDI, Indian J. Pediat. **20**:193 (Sept.) 1953.

The author presents a well-written discussion of electrolyte imbalance in diarrhea, with a consideration of the interpretation of the changes and the application of this knowledge to treatment. Electrolyte and fluid balance must be corrected before dietary regimens are begun.

McGUIGAN, Evanston, Ill.

ULTRAVIOLET FLUORESCENCE OF TONGUE IN AFRICAN CHILDREN. BERNARD T. SQUIRES, South African M. J. **27**:759 (Sept. 5) 1953.

Fluorescence of the tongue has previously been described, and related by some investigators to the bacterial production of porphyrins. Examination of 873 African and 44 European children of school age showed fluorescence in 51% of the Africans, as opposed to 40% of the Europeans. Nine per cent of Africans showed fluorescence over more than half the dorsum of the tongue, as opposed to 16% of Europeans, and 40% of Africans and 44% of Europeans showed less than half the tongue involved. No clinical conclusions are drawn.

McGUIGAN, Evanston, Ill.

ROENTGENOGRAPHY OF ABDOMEN AS AID IN DIAGNOSIS OF ACUTE INTESTINAL INTUSSUSCEPTION IN INFANTS. W. GALLUZZI and A. GIANELLI, Lattante **24**:296 (May) 1953.

Ten x-ray pictures are shown of the abdomens of infants with acute intussusception. These pictures indicate the existence of a spastic ileus. Final confirmation of the diagnosis may be made by a barium enema.

HIGGINS, Boston.

PUNCTURE LIVER BIOPSIES IN CHILDREN. G. SANSONE and F. DeMATTEIS, Minerva pediat. **5**:265 (April 30) 1953.

The technique, indications, contraindications, and safety precautions in taking liver biopsy specimens by the needle-puncture method are discussed. Seven case histories are given, with illustrations of histological material obtained by liver puncture.

HIGGINS, Boston.

LAST DAYS OF A BOY WITH CYSTIC FIBROSIS OF THE PANCREAS. G. FIORAVANTI and D. PERBELLINI, Minerva pediat. **5**:291 (April 30) 1953.

The terminal episodes in the case of a boy 28 months old with cystic fibrosis of the pancreas were largely respiratory. There were dyspnea due to bronchial secretions, bronchiectasis, staphylococcic lung abscesses, a paroxysmal cough, and high fever. Although there was marked cystic fibrosis of the pancreas, the islands of Langerhans were normal in appearance and in function.

HIGGINS, Boston.

SO-CALLED ACUTE DISORDERS OF NUTRITION OF INFANTS. W. KELLER, Deutsche med. Wchnschr. **78**:623 (April 24) 1953.

The author classifies acute diarrheal diseases of infants with disorders of nutrition as enteral and parenteral. The enteral forms are subdivided into alimentary conditioned forms and forms due to infection. The parenteral forms are referrable to focal infections, for instance, "otogenous," or to general infections. The role of pathogenic colon bacilli is discussed.

AMBERG, Rochester, Minn.

CASE OF CHRONIC INTUSSUSCEPTION. R. VANHEULE, Maandschr. kindergeneesk. **21**:86 (March) 1953.

The author describes a case of chronic intussusception of the intestine characterized by its long duration, the extreme atrophy caused by the lesion, and the unusual roentgenological picture.

FROM THE AUTHOR'S SUMMARY.

Nervous Diseases

CONVULSIONS IN CHILDHOOD. N. S. TRIBEWALA, Indian J. Child Health **2**:575-579 (Dec.) 1953.

Causes of convulsions in childhood are described, and differential diagnosis is outlined. Anticonvulsant drugs are discussed, though none other than phenobarbital, paraldehyde, magnesium sulfate, chloral hydrate, and bromides are mentioned.

McGUIGAN, Evanston, Ill.

SPONTANEOUS SUBARACHNOID HEMORRHAGE IN AN INFANT OF TWO MONTHS. J. R. VALLE and A. R. CAVALCANTI, J. Pediat. **18**:392 (Oct.) 1953.

The authors present a fatal case of subarachnoid hemorrhage due to a spontaneous rupture of a congenital aneursym of the basilar artery in a 2-month-old girl. It is believed this is the youngest of such clinical cases ever reported.

FROM THE AUTHORS' SUMMARY.

RECURRENT MENINGITIS DUE TO INFANT OTITIS. H. RICHTER, Deutsche med. Wchnschr. **78**:405 (March 20) 1953.

A girl 7 months of age was treated with penicillin for a purulent meningitis at a time of transitory symptoms of a light acute inflammation of the middle ear. Six days after recovery, the first recurrence of severe meningitis yielded to the same therapy in seven days. A second recurrence supervened, clearing in five days under treatment, only to be followed by a third recurrence, this time with purulent discharge from the left ear. In connection with the antrum, a small cavity full of pus was found. Its evacuation was followed by recovery in three weeks.

AMBERG, Rochester, Minn.

News and Comment

ANNOUNCEMENTS

Pediatric Postgraduate Refresher Course.—The annual pediatric postgraduate refresher course at Tulane University of Louisiana School of Medicine this year will be devoted to "Pediatric Therapeutics"; Dr. Henry G. Poncher will be the guest speaker. The program will be under the direction of Dr. Ralph V. Platou and will last from Monday, Feb. 7, 1955, at 8:30 a. m., through Friday noon, Feb. 11, 1955. Specific therapeutic approaches for a wide variety of pediatric problems will be considered, with many members of the faculty participating. Registration will be limited to 40 qualified specialists in pediatrics. Those interested should contact Dr. C. G. Grulee Jr., Division of Graduate Medicine, 1430 Tulane Ave., New Orleans 12.

PERSONAL

Appointment for Dr. William C. Adams.—Dr. William C. Adams, of Ridgewood, N. J., has been appointed Instructor in Child Health to the full-time faculty of the University of Louisville.

CORRECTION

In the August, 1954, issue of the A. M. A. American Journal of Diseases of Children, page 284, the price of the "1953-1954 American Pediatric Directory" should be listed as $10.00.

Books

Probleme der Schutzimpfung und die Bekämpfung der Rindertuberkulose. By G. Ramon. Price, 7.20 Deutsche marks. Pp. 51. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart-O (American Zone); Agent for U. S. A.: Grune & Stratton, Inc., 381 4th Ave., New York 16, 1952.

The book, a monograph within a series, the Tuberculosis Library, is neat in appearance, its print and paper are of good quality, and there are no typographical errors (Page 8, fifth line, should probably read "virulenz" instead of "resistenz"). It is intended for use by veterinarians, as its title indicates ("Problems of Immunization and the Fight Against Bovine Tuberculosis").

The following review of the contents of the book does not reflect the personal opinion of the reviewer.

The first of the two sections deals with "Allergy and Immunity." Ramon reminds his readers of a number of immunization experiments wherein killed tubercle bacilli had been employed; he does not consider them entirely without merit. Turning next to (live) vaccines of the type of BCG, he concedes them a certain value. They are, however, afflicted with the disadvantages of live vaccines in general. The present innocuousness of BCG, if properly prepared according to directions of Calmette and Guérin, is not questioned. Among the problems in the manufacture of the vaccine, the writer lists the difficulty of reaching and maintaining a virulence optimum, the absolute need for avoidance of contamination (no preservatives should be added to live vaccines), and the limited keeping qualities of the fresh vaccine. He also considers the dosage employed as rather crude, since it can be estimated only in terms of milligrams, and as such does not convey a measure of its immunizing power.

Regarding immunity following vaccination against tuberculosis, the fact is lamented (and in that everybody will agree with him) that there is no simple test to measure immunity. In the absence of such a specific test to indicate immunity, the tuberculin test is used and its result taken as an expression of resistance against tuberculosis. Various conflicting opinions with regard to the relation of allergy and immunity are quoted. There is no necessary correlation between allergy and immunity; the one can exist without the other.

After quoting various recent editorials from the American medical literature reflecting the present attitude of the American Medical Association Council on Pharmacy and Chemistry, the American Trudeau Society, and the United States Public Health Service, Ramon expresses his opinion that the problems of immunization against tuberculosis have not been solved at the present time. Efforts, in his opinion, have to be increased to improve BCG or to replace it by a vaccine which is more easily prepared, applied, and at the same time more effective. He is obviously referring to the "chemical vaccines" of Pasteur.

The second section deals with the problems of prophylactic immunization and sanitary regulations. Early experiments of Calmette and Guérin are mentioned which were indeed successful and promising. Calmette's own evaluation is quoted, indicating that a true immunity had been achieved and that its duration, just as with other live vaccines, is more or less persistent, depending on the nature, quality, and virulence of the organisms employed. The good early results of Calmette and Guérin, which later on could not be reduplicated, are thus in part explained by the fact that the bacteria used had a relatively higher virulence (and thus a greater antigenic power), since they had not undergone too many transfers.

Leaving the laboratory aspects, the author mentions some practical attempts at evaluation of BCG in cattle. Dalling arranged for two separate experiments. In the first experiment, 25% of the vaccinated animals proved tuberculous, as contrasted with the 52% among the unvaccinated controls, some of which were severely affected. Thus a remarkable though not complete resistance had been produced by BCG. The second experiment, which was tried to determine whether whole herds could be protected against tuberculosis by BCG vaccination alone, did not turn out

to be entirely successful. Thirty per cent of the vaccinated animals showed signs of tuberculosis at autopsy. The involvement was extremely mild, though, the tuberculous manifestations being restricted to the retropharyngeal, mediastinal, and mesenteric lymph nodes.

Kaplan, who conducted a project in Poland under the auspices of UNRA, summarized his results as follows:

1. Repeated vaccination of calves proves effective in protecting such animals up to the age of 2 years. Subsequently, immunity declines in spite of renewed vaccination.
2. Vaccination with BCG in grown-up animals is not protective.
3. Vaccinated calves must be removed from an infected environment.
4. Animals with advanced tuberculosis must be removed from the herds immediately, and all tuberculin reactors should be replaced by vaccinated animals as soon as feasible.

The results of previous experiments by Flückiger, which confirms Kaplan's findings, are likewise recorded. Thus the practical results of immunization in cattle have proved only relatively successful. Besides, the difficulties in carrying out and supervising (follow-up) an immunization program in cattle and the implications with regard to the tuberculin test are mentioned.

In the fight against infectious diseases of cattle and man, immunization procedures represent only one weapon. The other main weapons are general hygiene and sanitary regulations. With regard to the latter, two main methods are mentioned: (1) the radical (stamping out) method which has proved so successful in the United States and by which cattle herds have largely been freed of tuberculosis; according to this method, all cattle are systematically tuberculin tested and all reactors slaughtered, and (2) the Danish method (Bang method); this method likewise uses the tuberculin test and recommends the slaughtering of all reactors; however, it permits their being kept under strictest separation if their immediate slaughter does not seem feasible for economic reasons. The author goes along with these sanitary measures and is no longer in favor of BCG immunization in cattle. To support his view he quotes various resolutions adopted at sessions of the international office of epizootics of which he, incidentally, is the president. Participants at the 16th session (in 1948) of the international office of epizootics went on record essentially as follows:

> At previous sessions BCG immunization under official supervision had been recommended. During a 16-year period, no report shedding light on the practical results with BCG immunization has been received. On the other hand, sanitary measures employed by various countries in the fight against tuberculosis have proved successful.

It goes without saying that methods employed in veterinary and human medicine must by necessity be different. It is doubted that the American reader will gain any essentially new information from this book.

Manuel Pratique de Vaccination par le B.C.G. By R. Mande. Price, 950 French francs. Pp. 200, with 43 illustrations, 40 which are in color. Masson & Cie, 120 boulevard Saint-Germain, Paris, 6e, 1954.

This manual of BCG vaccination is published under the auspices of the International Children's Center, situated in Paris. It attempts to present as simply and as practically as possible the conditions under which one may obtain the best results with BCG vaccination. As stated in the foreword by Professor Debré, Dr. Mande has not only worked at the pilot station of the International Children's Center, but has also worked in the field in France, as well as in North Africa. In his "Introduction" chapter, the author reviews some of the well-known studies on BCG vaccination. From these studies as well as his own, he concludes that BCG is harmless and that it confers a degree of protection against superinfection with virulent tubercle bacilli. He points out that the immunity conferred by BCG differs from that conferred by a virulent primary infection in that with the latter, virulent organisms enter the body and can always be the source of active disease. In the second chapter, on the "Selection of Subjects to Vaccinate," he reviews the various methods of tuberculin testing, giving the actual method employed and the results obtained. Several photographs are shown illustrating the method of administration as well as the results obtained. He recommends that only those who are tuberculin negative should be vaccinated.

In the third chapter, under "The Vaccination," the author discusses the vacine, both the fresh and the dry, and points out that the results obtained by the two types of vacine are practically the same. The various methods of vaccination are discussed, such as the multiple puncture, scarification, and intradermal methods. The subcutaneous and oral methods have been practically abandoned. The actual techniques of these methods are given, and photographs of the results obtained are presented. Various indications and contraindications are discussed. Isolation is recommended where there is a possibility of exposure to active disease.

In the fourth chapter, on the "Followup after Vaccination," he points out that the vaccination alone is not sufficient. The development of the tuberculin reaction and its significance is discussed. Factors which influence the reaction are considered as well as the indications for revaccination.

In the fifth chapter, "Incidence or Accidents Accompanying Vaccination" are discussed. Both the nonallergic and the allergic or preallergic persons are considered. Although complications are exceedingly rare, they do occur, and differences have been noted in various parts of the world which may depend on technique as well as on the population itself. Thus, in the pilot station of the International Children's Center in Paris, only 2% of the infants developed suppuration of the draining lymph nodes following the intradermal method of vaccination; 8.6% developed this complication in mass vaccinations in Algiers. There is a greater incidence of local complications at the site of inoculation if vaccination is done in allergic or preallergic persons.

In Chapter 6, "The Manifestations of Tuberculosis Observed in Subjects Vaccinated with BCG," the author differentiates between those who are infected with virulent organisms before immunity sets in and after immunity sets in. From the literature and from his own studies of some 12,641 cases at the pilot station, he concludes that BCG does not alter or aggravate the course of a primary infection if the two are initiated at approximately the same time. If the virulent infection occurs after immunity has set in, it can be detected by a marked augmentation of the tuberculin reaction and/or clinical and x-ray findings. The incidence of virulent superinfection, however, as deduced from the literature and from their own follow-up of two years, is much less in the vaccinated than in the controls. Other problems of differential diagnosis, especially certain bronchopulmonary lesions, are discussed.

The last chapter, "Essential Principles of Vaccination with BCG," is a review of the technique and indications and contraindications. These 11 pages summarize the practical aspects of vaccination.

This manual is directed toward the practitioners in France and its colonies and stresses the methods employed there. A previous book by the same author and Huet, A., (Le Centre International De L'Enfance, Study No. 3, Paris, 1952) is recommended for more fundamental studies on BCG vaccination.

Personality Development in Adolescent Girls. By Lawrence K. Frank, Ross Harrison, Elizabeth Hellersberg, Karen Machover, and Meta Steiner. Price, not given. Pp. 316, with 25 illustrations. Child Development Publications, Louisiana State University School of Medicine, New Orleans, 1953.

This is a very interesting study by indirect (projective) methods of the way girls at various stages of adolescence think and feel about themselves and the world around them. The subjects were 300 girls, equally divided into three groups: (1) prepuberal, 10.6 to 14.5 years of age, who had not yet reached the menarche, (2) puberal, 10.6 to 15.5 years of age, who had recently begun menstruation, (3) adolescent, 17 to 19.11 years of age, who had established menstrual cycles and had presumably passed the menarche several years earlier. They came from all social-economic levels, although there were proportionately somewhat more from the middle and upper than from the lower economic groups. The published figures are not complete, but it appears that there is a somewhat greater number of girls from Jewish family backgrounds than is true of the population as a whole. The girls were taken by entire school classes to avoid, as far as possible, the process of selection. They were given four of the best known projective tests, Rorschach, T.A.T., Horn-Hellersberg, and Draw a Figure, and, in addition, their handwritting was analyzed. The examiners are recognized leaders in the field of clinical psychology. Although

no examination of 300 girls (actually 100 in each subgroup) can be considered definitive as far as all girls of similar age are concerned, the findings are of great interest and deserve serious thought and further confirmation.

One of the most striking findings is that between 25% and 30% of girls from all ages and classes show a fairly serious degree of emotional disturbance. Most of them seemed unhappy, and almost all were having difficulty in accepting being girls and, subsequently, women. Their concept of womanhood is of the glamour-girl variety, rather than of a responsible maternal woman. Some of this is certainly a product of their chronological age, but some seems to be related to other things, perhaps the changing cultural concept of woman's fundamental role as mother and homemaker to that of an economic competitor with man.

The best-adjusted girls were those few girls from the lower social-economic group who had escaped the sexual traumatization so common to girls of this group. In speaking of the others, the authors say, "In all these social-economic levels, higher intellectual capacity and performance seem to counteract or block acceptance of the feminine role. . . ." They add, "It appears that these girls are caught in a conflict between maturing as young women and their almost compulsive need to conform, to win approval." There are some indications that during the time just before and just after puberty, girls are so involved in their own internal changes, in feelings about themselves and their relations to others that they are relatively incapable of meeting the demands of schools for sustained study and academic achievement. It is suggested that very little in the way of academic requirements be demanded of girls at this very trying time in their development.

These are perhaps the highlights from this study. Much of the discussion of the details of test performance will be relatively unintelligible to the unpsychological sophisticated physician, but the conclusions and suggestions demand the thoughtful consideration of all pediatricians.

There is an urgent need to know, by other careful studies, if the findings here reported are truly representative of most adolescent girls in this country. If so, it is something with which every thoughful citizen should concern himself as it could mean even further instability in family life as these girls marry and more and more children grow up without the maternal support necessary for healthy emotional development.

The Diagnosis and Treatment of Convulsive Disorders in Children. By S. Livingston. Price, $9.50. Pp. 314. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1954.

Dr. Livingston has presented an excellent and complete book on the practical aspects of the convulsive disorders in children. The book will be extremely useful to every general practitioner and pediatrist. There are a number of pertinent statements, such as "an electroencephalographic examination should be performed when a diagnosis cannot be established by the usual clinical and laboratory investigations." He has a very sensible evaluation of the hypoglycemic convulsions. In the treatment of convulsions, the author advises against the use of ether if there is an acute disease of the respiratory tract. There is some question as to whether ether should ever be used. The symptomatology and the neurologic findings in cerebral birth injuries might have been enlarged. It is rather surprising that the author has found the ketogenic diet effective in congenital developmental diseases of the brain. He has also had success with the diet in the treatment of other organic cerebral lesions. Febrile convulsions are considered in detail and properly evaluated. The author reviews the controversy concerning narcolepsy. Akinetic seizures are discussed in their proper perspective. They present the typical electroencephalographic findings which have been more recently designated as "hypsarrhythmia." There is a difference of opinion as to the significance of so-called "abdominal seizures" in true idiopathic epilepsy. Children are subject to so many abdominal pains of such diverse etiology that a true diagnosis is almost impossible. The fact that the pain is relieved with phenobarbital has little significance. Most of the electrograms presented as evidence of epilepsy in such cases are open to question. It is doubtful whether emotional disturbances play a significant part in the precipitation of epileptic seizures. The relationship of allergy to epilepsy is extremely distant and questionable. The author has found no definite evidence. It is well that the author quotes the original observations on hyperventilation by Rosett and Foerster. There will be a difference of opinion with the author's conclusions that pneumoencephalography has any value in diagnosis or in treatment of children with convulsive seizures. A number of patients have been entirely free

of seizures following air studies when they were used as a last resort. The author has a good familiarity with electroencephalography and uses the procedure to its fullest advantage. He states that "It is important that the limitations of electroencephalography in children be appreciated, otherwise much serious misunderstanding will continue." At the present time some imaginative interpreters are even attempting to outline treatment of the epileptic patient on the basis of the findings on one 20-minute run or tracing.

The author's general plan of treatment is well divided into drug therapy and dietary therapy. Fortunately, his excellent judgment presents the established drugs in their proper sequence. He is one of the few investigators who is using bromide to any extent. The recent publicity announcing glutamic acid as a new advance in the treatment of epilepsy is properly disposed of in three-fourths of a page. Reference is made to the original article, in 1943, and to the fact that no results of any consequence were observed in the treatment of convulsions or in the improvement of the intelligence quotient. The author has found the ketogenic diet to be the most useful treatment of epilepsy today, with the highest percentage of favorable results. This reviewer believes that his treatment would be more effective if he carried the preliminary fast to 10 days or 2 weeks, whenever possible. The short paragraph on the surgical treatment of epilepsy, by A. A. Walker, is a useful addition. Apparently the limitations are great. The book is profusely illustrated and well printed.

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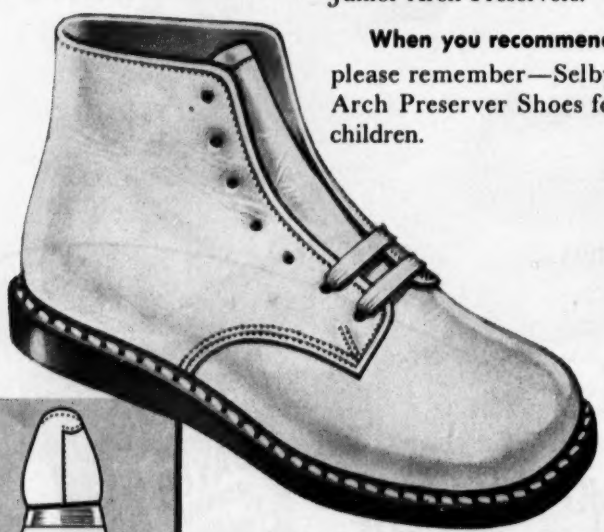

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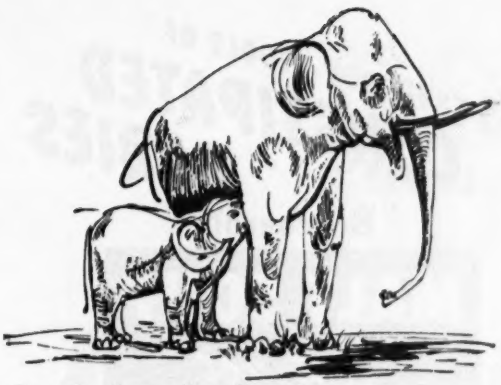

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1. Lampert, L. M.: Milk and Dairy Products, Brooklyn, Chemical Publishing Co., Inc., 1947, p. 10.
2. Gunther, M.: Brit. J. Nutrition *6* (No. 2): 215, 1952.

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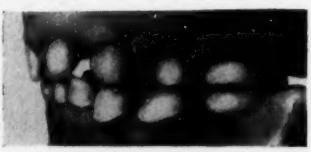

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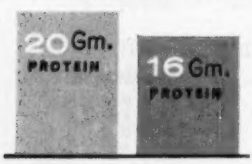

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1. Jeans, P. C., in A.M.A. Handbook of Nutrition, Philadelphia, Blakiston, 1951, pp. 275-298. 2. Stare, F. J., and Davidson, C. S., in The Proteins, American Medical Association, 1945.

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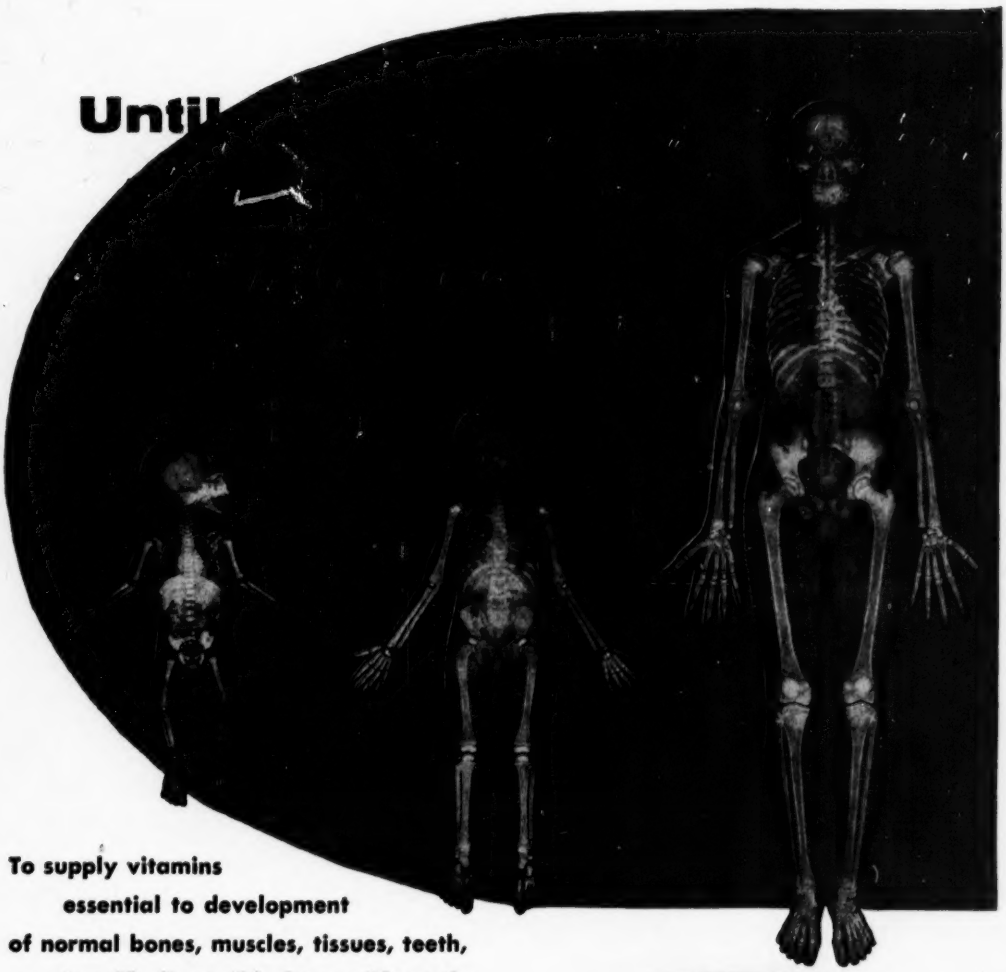

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